UNIVERSITY OF MICHIGAN
MAY 5 1955
MEDICAL

Vol. 43 · July 1954 · No 4

INDEX

Retarded Growth in Association with Gonadal Insufficiency. Three Cases of Turner's Syndrome 311
J. Öster
Plasma Glutamic Acid in Children with Brain Diseases as Compared with Normal Children 320
I. Munkvad and J. Vesterdal
Appearance of the Fundus Oculi in Prematurely Born Infants Treated With and Without Oxygen 327
A. Huggert
Amino-Aciduria in Galactosaemia 337
S. Darling and O. Mortensen
Plasma Electrolytes in the Neonatal Period 342
Th. Strengers, J. W. Maas, H. Rottinghuis and G. A. Fehmers
Primary Vitamin D Refractory Rickets. I. Report of Two Cases Treated with High Doses of Vitamin D 347
J. Winberg, C. G. Bergstrand, B. Engfeldt and R. Zetterström
Breast or Cow's Milk as Infant Food. Discussion on the Methods of Comparison . . 362
G. v. Sydow and N. Faxén
Infants of Diabetic Mothers. I. Foetal Hypoxia in Maternal Diabetes. 368
G. Berglund and R. Zetterström
Periarteritis Nodosa in an Infant of Three Months 374
M. Bohman
Megaloblastic Anemia in Infancy. Megaloblastic Anemia Occurring in an Infant of a Mother Suffering from Pernicious Anemia of Pregnancy 379
R. Zetterström and S. Franzén
La maladie des griffes du chat (Cat Scratch Fever) 386
R. Debré and J. C. Job
Studies in Diabetes Mellitus 389
G. Engleson
The Resistance of Red Cells in Vitro 390
S. Sjölin
Proceedings of the Section for Pediatrics and School Hygiene of the Swedish Medical Society, April 9 and May 29, 1954 393
Book Reviews 397
News and Comments 398

Almqvist & Wiksells Boktryckeri AB UPPSALA

ACTA PÆDIATRICA

Chief Editor PROFESSOR A. WALLGREN
Karolinska Sjukhusets Barnklinik, Stockholm 60

Co-Editor PROFESSOR BO VAHLQUIST
Akademiska Sjukhuset, Uppsala

REDACTORES:

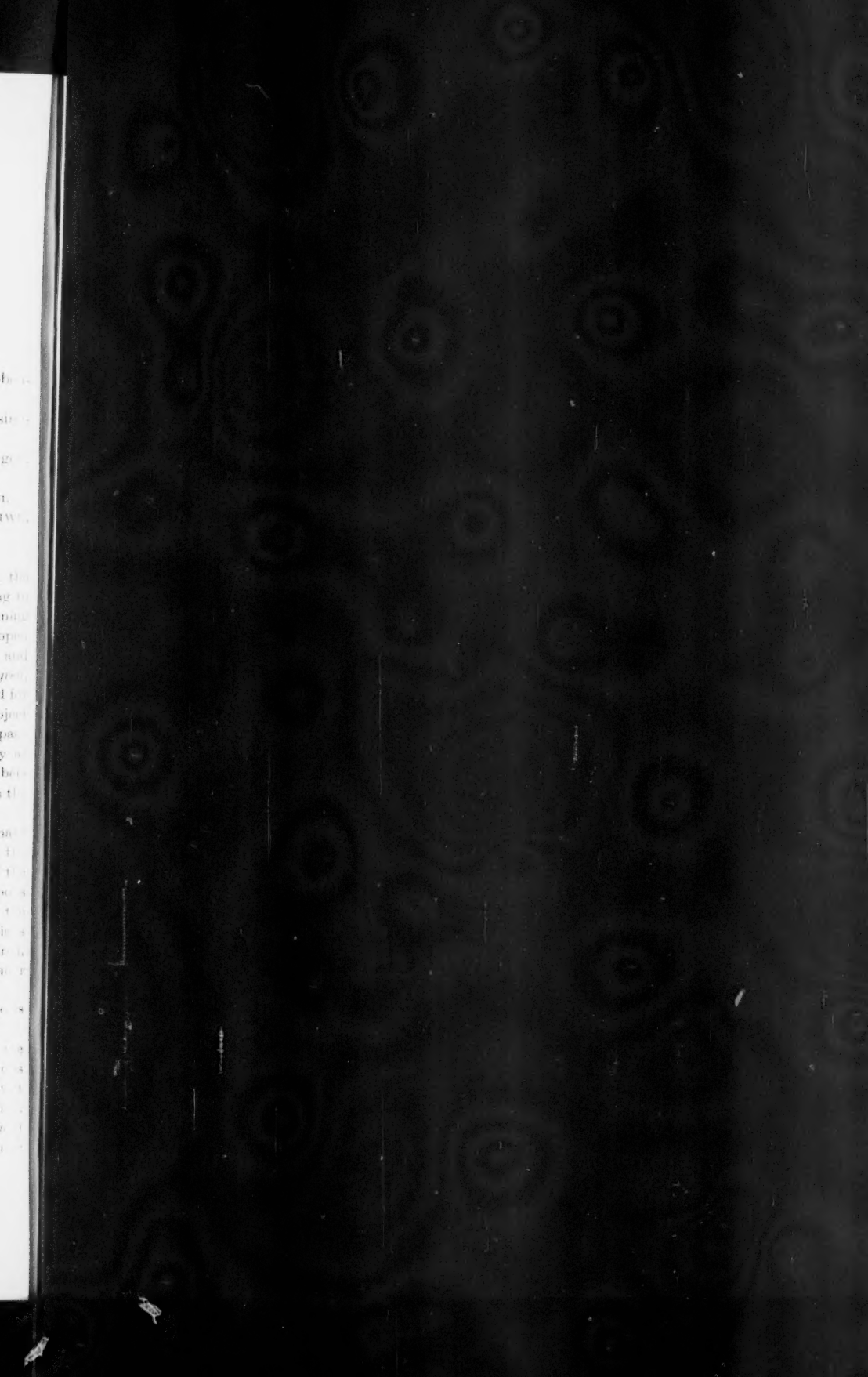
In Dania: BENT ANDERSEN, Aarhus, OLUF ANDERSEN, København, P. PLUM, København.
In Fennia: P. HEINIÖ, Helsingfors, V. RANTASALO, Helsingfors, C.-E. RÄIHÄ, Helsingfors, T. SALMI, Åbo, ARVO YLPPÖ, Helsingfors.
In Hollandia: S. VAN CREVELD, Amsterdam, J. VAN LOOKEREN CAMPAGNE, Groningen, J. P. SLOOFF, Eindhoven.
In Norvegia: LEIF SALOMONSEN, Oslo, L. STOLTENBERG, Oslo, A. SUNDAL, Bergen.
In Suecia: C. GYLLENSWÄRD, Stockholm, N. MALMBERG, Stockholm, STURE SIWE, Lund, WILHELM WERNSTEDT, Stockholm, Y. ÅKERRÉN, Göteborg.

The ACTA PÆDIATRICA publishes papers on scientific and clinical investigations in the field of pediatrics. These papers are published in English, French, or German, according to the wishes of the author. Each number consists of about 5–6 printed sheets, 6 numbers forming one volume. The numbers will be issued every second month. The Acta Pædiatrica is open to papers from authors in all countries. Manuscripts for publication, books for review, and correspondence relating to the editorial management should be sent to *Prof. Arvid Wallgren, Chief Editor, Karolinska Sjukhusets Barnklinik, Stockholm 60, Sweden.* Papers are accepted for publication on condition that they are contributed solely to the Acta Pædiatrica. They are subject to editorial revision. The paper should preferably not exceed 16 printed pages including space for figures and tables. Monographs and more extensive articles are published separately as supplements at the author's own expenses. These supplements will be delivered to subscribers free of charge. Manuscripts are published in the order received, but the Editor reserves the right to change this order when advisable.

Manuscripts should be type-written, double spaced with reasonably wide margins. A summary should be included. A complete bibliography must be added and must conform exactly to the style of the *Quarterly Cumulative Index Medicus* giving name of author, initials, full title of the paper, and abbreviated name of the journal, with volume, page, and year. References to books and monographs should indicate the author, the title, the name and city of the publisher, the year of publication, and the edition. References must be listed alphabetically. Illustrations (marked with the author's name) and tables accompanying manuscripts should be numbered, provided with suitable, short legends and so arranged that they are comprehensible to the reader without reference to the text.

Tables and figures that exceed 3 pages in the original papers and 2 pages in the case reports are printed at the expenses of the author.

Galley proofs will be sent to the principal author from the printer to be returned to the Editor together with the manuscript when corrections are completed. Reprints of articles published must be ordered specifically in separate communications to the publishers Almqvist & Wiksell, Uppsala, Sweden. All communications in regard to advertising, subscription, change of address, etc., should also be sent to the publishers. Checks, money orders, and drafts should be made payable to the publishers. Subscription price Sw. cr. 45:— pr volume, postage included.



Acta Pædiatrica **43**: 311—319. July 1954

From Dronning Louise's Børnehospital
(Prof. Oluf Andersen, M.D.)

Retarded Growth in Association with Gonadal Insufficiency

Three Cases of Turner's Syndrome

by JAKOB ØSTER

Since the end of the 19th century considerable interest has been displayed in the medical problem of dwarfism—especially in childhood. We must admit, however, that patients with retarded growth are very often difficult to classify, the genesis being obscure. The numerous causes of retarded growth in length, or dwarfism, will not be mentioned in this article. Nor is it possible to review briefly the differential diagnoses in cases of dwarfism. Those interested in the question are referred to the large manuals (e.g. Wilkins 1950). The importance of the problem in mongolism has previously been discussed by the author; and an account has been given elsewhere of the differential diagnosis of hypothyroid dwarfism from the chondrodystrophies. In particular, attention has been called to the characteristic epiphyseal dysgenesis occurring in hypothyroidism.

In the present paper mention will only be made of certain hormonal findings of importance for the differential diagnosis in some forms of retarded growth. In *pubertas praecox* we find a normal excretion of gonadotropins, and increased or normal excretion of 17-ketosteroids in the urine. In *anterior pituitary dwarfism* the excretion of both gonadotropins and 17-ketosteroids is low. Finally, in *ovarian agenesis*—which will be further described below—gonadotropins are excreted in large amounts and 17-ketosteroids in small amounts. In addition, we find here a low excretion of androgens.

These hormonal disturbances are explainable by the underlying disease. In anterior pituitary dwarfism with attendant gonadal insufficiency the latter is secondary and due to a reduced production of anterior pituitary gonadotropin. In ovarian agenesis—and testicular dysgenesis—the disturbances are due to a primary defect of the gonads. The high excretion of gonadotropins seen in cases of ovarian agenesis is probably accounted for by the absence of an inhibiting action on the pituitary body by the ovaries, normally existing in females after the age of 11 or 12. In this latter disease, the cause of the dwarfism is hardly the reduced oestrogen production owing to the

UNIVERSITY OF MICHIGAN LIBRARIES

ovarian agenesis, because patients castrated before the age of puberty grow tall and eunuchoid. It is here rather a question of a genetically determined dwarfism.

TURNER in 1938 described "a syndrome of infantilism, congenital webbed neck, and cubitus valgus". He presented seven girls between the ages of 15 and 23, who all displayed infantilism, i.e. retarded growth and sexual underdevelopment, webbed neck, and cubitus valgus. He emphasized that the shortness of the neck is apparent only, since there has never been found coalescence of cervical vertebrae—as may be seen in Klippel-Feil's disease. VARNEY *et al.* (1942) found a relationship between Turner's syndrome and high excretion of gonadotropin in the urine. They named the condition "ovarian dwarfism". Since then Turner's syndrome with ovarian agenesis has often been mentioned in paediatric-endocrinological literature. In this connection reference may be made to CAFLICH (1952), who has made an excellent review of the literature, together with a report of his own cases.

Of Scandinavian writers who have mentioned Turner's syndrome the following may be mentioned: HOJER (1945), KALJSER (1948), HAMNE (1948), VAN CREVELD and WAHL (1949), HORSTMANN (1949), and GRANRUD (1952), as well as VAN BUCHEM (1952). Further, it is likely, according to the description, that HESS THAYSSEN's (1934) patient and some of NIELSEN's (1934) patients with dystrophia brevi-collis suffered from this disease.

A syndrome with gonadal insufficiency seems to occur in males, too, as there have been described male patients with webbed neck, retarded growth, cubitus valgus, and genital hypoplasia with testicular atrophy or hypoplasia. FLAVEL (1943) described the first case, which, however, is not definite, because the patient, a man aged 21, who presented webbed neck, and cubitus valgus, as well as feminine stature, had normal erections and emissions. In GREENBLATT and NIEBURG's (1948) case—a male patient with typical Turner's syndrome—biopsy revealed azoospermia with hypoplasia of the seminiferous tubules and increased number of interstitial cells. There was found normal serum gonadotropin, and the 17-ketosteroid excretion was normal. DORFF's (1948) patient—a 3-year-old boy—presented webbed neck and underdeveloped genitals with undescended testicles. Though the diagnosis cannot be made with certainty at this young age, this case is likely to have been an instance of the disease. Finally, CUNNINGHAM and HARLEY (1951) described a 7-year-old boy of small stature, with webbed neck, and undescended testicles, as well as bilateral ptosis and mild micrognathia. These various signs suggest a diagnosis of Turner's syndrome. Gonadotropin and 17-ketosteroids were excreted in normal quantities. CAFLICH (1952) mentions several cases from the literature of Turner's syndrome in male patients, but they are doubtful or difficult to assess.

Two cases of Turner's syndrome in girls and one—more doubtful—in a boy will be described below.

Case 1. Case 451/52, girl, born June 17, 1938. She is the first of three sibs. No dwarfism or sexual infantilism in the family. She was born 4 weeks before term, by

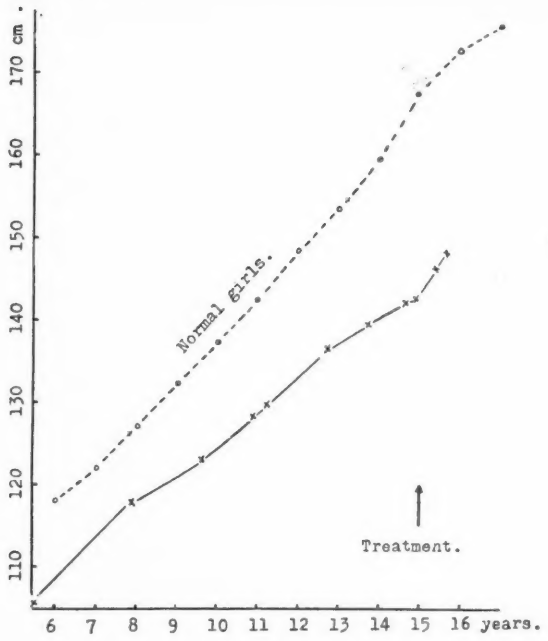


Fig. 1. Growth of the girl (Case 1).

natural delivery. Birth weight 3250 g and birth length 51 cm. She was asphyctic with the cord around her neck. She was admitted to hospital first at the age of 10 months, presenting the following pathological signs: hoarse voice, open mouth, bilateral epicanthus, ptosis of the left upper eyelid, as well as a high narrow palate, and strikingly short limbs.

She has since been admitted several times. At the age of 5 years she was admitted on account of transitory haemorrhage per rectum. At the age of 6 she was operated on for the pronounced leftsided ptosis, with a poor result. Her retarded growth in length was first noticed when she was 10 years old (Fig. 1). This was further accentuated during the following years. At the age of 13, the 24-hour gonadotropin excretion in the urine was found to be over 50 mouse units; oestrogens were not demonstrable, and the excretion of 17-ketosteroids was normal (3.2 mg/24 hours).

She was again in hospital from April 16 to April 30, 1952 (Fig. 2). From this stay we have the following report: Height 142 cm, weight 46.9 kg. She presents a high degree of adiposity of a fairly diffuse distribution, though with rather large pads of fat in the flanks; no striae. All over the skin there are found small naevi vasculosi and minor fibromas. The neck is markedly webbed, and the hair line at the back of the neck tapers off to a point in three places—in two, growing out on the skin folds extending from the mastoid to the region of the clavicle. The neck is freely movable. The scalp presents excessive pityriasis.

Eyes: ptosis of left upper eyelid, bilateral epicanthus, bilateral blepharitis.—Fau-

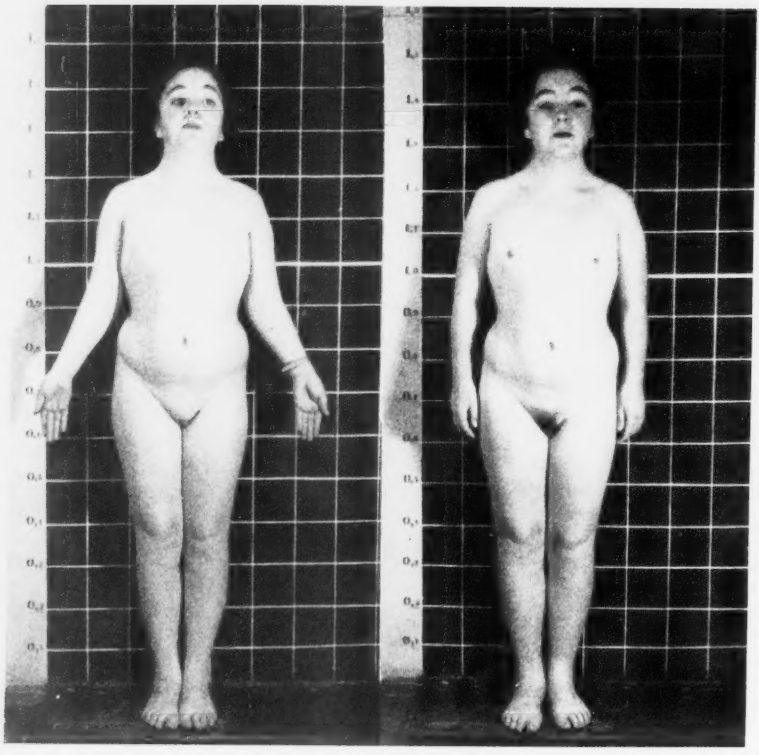


Fig. 2. Case 1 before and after treatment.

ces: high, narrow palate.—Ears: malformed, "crumpled", normally situated.—Steth. of lungs and heart: normal, especially no signs of any heart defect.—Abdomen: normal.

Extremities: pronounced cubitus valgus of both arms. Hyperflexibility of the finger joints, but limited flexibility of the joints of the first finger. Further, pad-like subcutaneous thickenings on the backs of the hands and fingers. Moderate lanugo on the forearms, but no pubic or axillary hair. The mammae not developed, the nipples are inverted, and the areolae not pigmented.

Her intellect is normal, but she seems somewhat embarrassed at not having developed like other girls of her age.

Gynecological examination: the vulva normal, the hymen present, the vagina could not be inspected. Rectal exploration: small uterus, no masses felt, and no ovaries palpable at the sides. Rectoscopy 9 cm up, revealed a normal mucous membrane.

Other examinations: Various X-ray examinations revealed no osseous abnormalities, more particularly, the spinal column and ossification centres were found to be normal, and there was no osteoporosis. No signs of heart disease. ECG normal. B.M.R. 87–91–

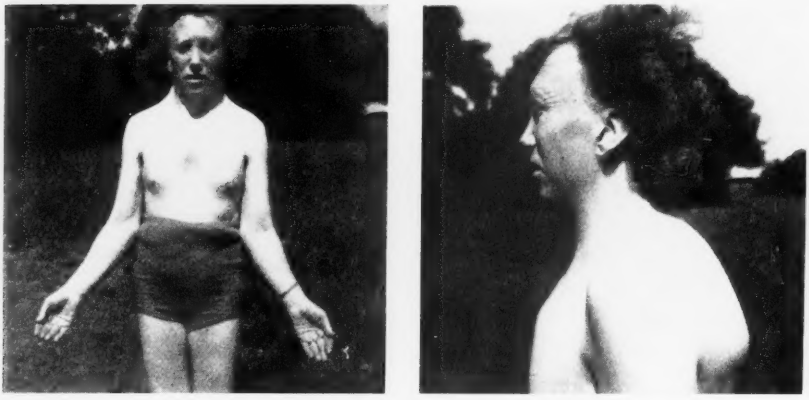


Fig. 3. Case 2.

91–87 per cent. Twenty-four hour hormone excretion in the urine: 17-ketosteroids 1.8 mg, gonadotropins over 50 M.U., oestrogens under 20 M.U., and androgens 8 I.U.

This being a typical instance of Turner's syndrome, presumably with ovarian agenesis, 10 mg crystalline Follicyklin (Ciba) were given intramuscularly each month. Under this treatment she grew taller (see growth curve), her mammae developed, the areolae became pigmented, and the nipples prominent. Pubic hair began to grow, but no axillary hair. After 7 months of treatment uterine bleeding occurred for the first time.

Case 2 (Fig. 3). Private patient 1952, born Dec. 2, 1919. She is the second of four sibs. Her parents and sibs are healthy. Birth weight 3500 g. Her nutritional progress was poor in babyhood, and her parents soon realised that she was both physically and mentally backward. Her retarded physical development became particularly noticeable towards the age of puberty. She stopped growing in length, and menstruation failed to occur. Her doctor tried hormone treatment with no effect. At the age of 14 she was admitted to hospital, where a diagnosis was made of mongolism and congenital heart disease. Has received disablement benefit since 1949.

Examination 1952: The patient is very small (140 cm), and she looks older than her age. She is strongly built and not feminine in appearance. There is a pronounced webbed neck with the hair line tapering to a point in three places at the back of the neck. The head movements are free, and X-ray examination revealed no coalescence of vertebrae. There is pronounced kyphoscoliosis of the thoracic part of the spinal column. There is pronounced cubitus valgus, bilateral epicanthus, and a high narrow palate. She has a marked funnel chest, no mammae, no axillary hair, and only scanty pubic hair.

On stethoscopy of the heart a loud systolic bruit was heard over the entire precordium. The nature of the congenital heart disease could not be defined during her stay in hospital. It is, however, not a coarctation of the aorta; there is no cyanosis nor dyspnoea.

The patient is mentally backward; she can read and write, practically without making mistakes. Her working capacity is greatly reduced, but she can help her mother with the housework.

UNIVERSITY OF MICHIGAN LIBRARIES

Fig. 4. Case 3.

Twenty-four-hour hormone excretion in the urine: oestrogens under 20 M.U., gonadotropins under 50 M.U., 17-ketosteroids 4.8 mg, or at the lower normal limit.

This is a case of an adult female patient presenting typical signs of Turner's syndrome, probably also with ovarian agenesis. She has never menstruated, and the rather low excretion of gonadotropins on a single examination naturally does not preclude this diagnosis, as the excretion may fluctuate round a mean value. A closer hormone control was impossible for various reasons. Treatment was omitted owing to the age and low intelligence.

Case 3 (Fig. 4). Case 257/52. Boy, born Jan. 4, 1942. An only child. His mother mentally backward. Pregnancy and delivery normal. Birth weight 3,500 g, birth length 49 cm. The boy began to walk and talk rather late. In 1947 he was operated on (decompression) because of premature cranial synostosis. A peculiar shape of the skull had already been noticed immediately after birth. He has always been smaller than other children of his age. His I.Q. was found to be 60, so that he is excused from compulsory school attendance.

Physical examination: height 116 cm (normal: 132 cm). He gives the impression of being feeble-minded. His forehead is very broad and prominent, and his head is dolicocephalic in shape. X-ray of the skull showed marked scaphocephaly and pronounced digital impressions. No visible sutures.

The eyes normal. The distance between the eyes rather wide, bordering on hypertelorism. — Fauces: delayed secondary dentition (but otherwise no signs of hypothyroidism). — Steth. of lungs and heart: normal. Mild funnel chest. — Abdomen: pea-sized umbilical hernia.

Genitals: small penis. Both testicles lie on a level with the external abdominal ring. A large left inguinal hernia was found.

Extremities: mild genua valga and moderate extension defect of the knee joints. Pronounced cubitus valgus, especially of the right arm. Both little fingers short and excessively crooked, and a very large distance between the first and the second toe.

Twenty-four-hour 17-ketosteroid excretion in the urine 1.5 mg, i.e. at the lower normal limit; 24-hour excretion of gonadotropins about 50 M.U., of oestrogens under 20 M.U., and of androgens just over 6 I.U.

Discussion and Conclusion

The three patients described above present, as stated, a great number of the signs and associated malformations grouped round the "webbed-neck disease", the pathogenesis of which has been thoroughly discussed by CAFLICH (1952), without, however, clarity having been obtained as yet regarding this problem.

The former two female patients quite obviously present Turner's syndrome with webbed neck, cubitus valgus, and infantilism. Although there is a definite relationship between gonadal insufficiency and growth inhibition in Turner's syndrome, we must not expect any great effect of the treatment on growth, because it is hardly a question of a causative relation. In cases of female patients with ovarian agenesis, it is nevertheless important that treatment with oestrogenic preparations be commenced at the age of 11 or 12, in order that the secondary sex characters may develop and menstruation be initiated. At this early stage, before the epiphyseal lines are closed, there is also a chance of increase in growth. Though injectable oestrogenic preparations presumably have the strongest effect, it is no doubt advisable, after menstruation has begun, to continue with oral administration for 3 weeks and then interrupt the treatment for one week, to provoke menstrual bleeding. WILKINS recommends further administration of progesterone during the last one of these 3 weeks of treatment, partly to stimulate the development of the mammae, and partly to imitate the hormonal conditions of the normal menstrual cycle as closely as possible.

The conditions relating to testicular insufficiency are still rather obscure, compared with those of ovarian insufficiency. The pronounced cubitus valgus, inhibited growth, very short and broad neck, and the oxycephaly, as well as the remaining minor associated defects in connection with oligophrenia, suggest a form of Turner's syndrome with primary testicular insufficiency in the case of the third patient, the boy. This disease must, like the ovarian

UNIVERSITY OF MICHIGAN LIBRARIES

agenesis, be regarded as genetically determined. Only relatively few cases of testicular insufficiency have been mentioned in the literature. It is no doubt a disease to which attention should be directed; and in this connection it is worth while to study the hormonal conditions and their relation to the results of testicular biopsies, which unfortunately could not be carried out in our case. Generally these patients seem to have sufficient androgen in their make up to give them a virile character. If not, substitution therapy must be considered.

Summary

Two cases are reported of Turner's syndrome in female patients. In addition, an account is given of a boy whose symptomatology highly suggests that he belongs pathogenetically to the same group. It is emphasized that therapeutic substitution therapy is definitely indicated in the cases of girls, though the pathogenesis is obscure. Further, it is pointed out that attention should be focused on testicular insufficiency in boys with a suspected Turner's syndrome, and that substitution therapy should be tried here, too.

Retard de croissance associé à une insuffisance gonadique. Trois cas de syndrome de Turner.

L'auteur rapporte deux cas de syndrome de Turner chez des malades de sexe féminin. En outre, il joint l'histoire d'un enfant, dont la symptomatologie est très évocatrice, et qui fait penser que celui-ci appartient au même groupe pathogénique. Il attire l'attention sur l'utilité de la thérapeutique de substitution surtout chez les filles, bien que la pathogénie soit obscure. En outre, il observe que l'attention doit être centrée sur l'insuffisance testiculaire chez les garçons suspectés de syndrome de Turner. La thérapeutique de substitution doit être essayée chez eux aussi.

Minderwuchs in Verbindung mit Geschlechtsdrüseninsuffizienz. Drei Fälle von Turner's Syndrom.

Über zwei Fälle von Turner's Syndrom bei weiblichen Patienten wurde berichtet. Ergänzend wird über einen Knaben berichtet, dessen Symptomatologie in hohem Grade vermuten läßt, daß er pathogenetisch zur selben Gruppe gehört. Obgleich die Pathogenese unklar ist, ist die Substitutionstherapie bei den beiden weiblichen Patienten indiziert. Weiterhin wird darauf hingewiesen, daß man bei Knaben mit fraglichem Turner Syndrom seine Aufmerksamkeit auf die testikuläre Insuffizienz richten und auch in diesen Fällen eine Substitutionstherapie versuchen sollte.

Retardo del crecimiento e insuficiencia gonádica. Tres casos del síndrome de Turner.

Se comunican 2 casos de síndrome de Turner en pacientes de sexo femenino. Se da cuenta además de un niño cuya sintomatología era altamente sugestiva como perteneciente al mismo grupo patogénico. Se insiste en que la terapéutica de substitución está claramente indicada en el caso de tratarse de niñas, aún cuando la patogenia de la enfermedad es todavía oscura. Se hace notar la necesidad de investigar una insuficiencia testicular en niños en quienes se sospecha un síndrome de Turner y de que también en estos casos debiera ensayarse la terapéutica de substitución.

References

VAN BUCHEM, F. S. P. *et al.*: Endocrine disturbances in coarctation of the aorta. Acta med. scandinav. *143:* 399, 1952.

CAFLICH, A.: Das Pterygium. Diss. Zürich 1952.

VAN CREVELD, S. and DE WAHL, O. M.: Case of ovarian agenesia. Acta pædiat. *37:* 474, 1949.

CUNNINGHAM, G. C. and HARLEY, J. T.: A case of Turner's syndrome. J. Pediat. *38:* 738, 1951.

DORFF, G. B.: Turner's syndrome in the male. Arch. Pediat. *65:* 555, 1948.

FLAVELL, G.: Webbing of neck with Turner's syndrome in male. Brit. J. Surg. *31:* 150, 1943.

GRANRUD, H., Syndroma Turner. Nord. med. *47:* 314, 1952.

GREENBLATT, R. and NIEBURGS, H. E.: Turner's syndrome. J. Clin. Endocrin. *8:* 993, 1948.

HAMNE, B.: Et fall av aortastenos och dystrophia brevicollis. Nord. med. *38:* 1135, 1948.

HOJER, N. T.: Ett fall av Turnersyndrom. Svenska läk.-sällsk. förhandl. *42:* 760, 1945.

HORSTMANN, P.: Dwarfism. Acta endocrin. Suppl. 5. Copenhagen 1949.

KAIJSER, K.: Et fall av dystrophia brevicollis. Acta endocrin. *3:* 351, 1949.

NIELSEN, H.: Dystrophia brevicollis congenita. Hospitalstid. *77:* 998, 1934.

OSTER, J.: Hypothyroid dwarfism in two brothers. Ugesk. Læger *115:* 1326, 1953.

Mongolism. A clinicogencalogical investigation comprising 526 mongols living on Seeland and neighbouring islands in Denmark. Danish Science Press Ltd., Copenhagen 1953.

THAYSEN, T. E. H.: Et tilfælde af dystrophia brevicollis congenita. Hospitalstid. *77:* 998, 1934.

TURNER, H. H.: A syndrome of infantilism, congenital webbed neck, and cubitus valgus. Endocrinology *23:* 566, 1938.

VARNEY, R. F. *et al.:* An association of short stature, retarded sexual development and high urinary gonadotropin. J. Clin. Endocrin. *2:* 137, 1942.

WILKINS, L.: The diagnosis and treatment of endocrine disorders in childhood and adolescence. Springfield, 1950.

Received 27.8. 1953.

Dronning Louise's Børnehospital
Copenhagen.

UNIVERSITY OF MICHIGAN LIBRARIES

Acta Pædiatrica **43**: 320–326. July 1954

From the University Clinic of Pediatrics (Chief: P. Plum, M.D.) and the University Clinic of Psychiatry (Chief: Villars Lunn, M.D.), Rigshospitalet, Copenhagen, Denmark

Plasma Glutamine and Glutamic Acid in Children with Brain Diseases as Compared with Normal Children[1]

by IB MUNKVAD and JØRGEN VESTERDAL

A number of papers have been published on the effect of glutamic acid administration in mentally retarded patients. Some authors have claimed that a beneficial effect on the IQ was observed, but this is, however, not very convincing, and other authors have been unable to demonstrate any effect. According to ZIMMERMANN & BURGEMEISTER and WAELSCH the varying results may be due to the fact that the clinical effect of sodium glutamate, which has been used by most authors, is less pronounced than that of the pure glutamic acid.

PRICE, WAELSCH & PUTNAM (1943) have found that glutamic acid has a therapeutic affect in some cases of petit mal, and this has been confirmed by other authors.

There is a theoretical basis for these clinical observations, in so far as glutamic acid is a very important substance in the metabolism of nervous tissue. WEIL-MALHERBE (1936) has demonstrated that glutamic acid is the only amino acid which is oxydized in the brain. Glutamine, which is the amide of glutamic acid, also plays a role in cerebral metabolism. After absorption from the intestine a deposition, particularly of the glutamine, takes place in the liver and the brain. Glutamine is split by an enzyme, glutaminase, into ammonia and glutamic acid. The latter is by another enzymatic process transformed to α-ketoglutaric acid. Both these processes are reversible. α-Ketoglutaric acid is a component of the tricarboxylic cycle of KREBS in the liver, brain and other tissues. This cycle is of primary importance in carbohydrate metabolism, and it is of special interest in the brain, where energy is derived exclusively from carbohydrates.

The blood levels of glutamine and glutamic acid give no direct information about the metabolism of the nervous tissue, as these substances are metabolized also in other tissues. However, if it were possible to demonstrate

[1] Supported by a grant from King Christian X's Foundation.

abnormal blood levels of these substances in patients with brain disorders, might provide a basis for further investigations.

Only a few observations on the content of glutamic acid and glutamine in plasma, have as yet been published. With the method of KREBS the following normal values have been found in adults: Glutamic acid 2.30 ± 0.59 mg per cent, and glutamine 7.68 ± 1.02 mg per cent (MUNKVAD 1951). Somewhat similar values were published by KREBS in 1949.

In adult patients with psychoses, especially schizophrenia, MUNKVAD has demonstrated lower plasma levels of glutamine, particularly in early cases. In epileptics the glutamic acid level was low in phases of the disease associated with frequent attacks and the glutamine level was increased.

As no investigations in this field have been done in children, we have made the following study on the plasma glutamine and glutamic acid in normal children as well as in children with cerebral disorders, particularly cerebral palsy and epilepsy.

Method

We have used the method of KREBS (1948) for the determination of glutamine and glutamic acid. This method is based on enzymatic break down of these two substances by means of glutaminase and *l*(+)glutamic acid decarboxylase (obtained from Chlostridium Welchii), by which process ammonia and carbon dioxide are formed. The carbon dioxide is determined in a Warburg apparatus, and the ammonia is measured by the Conway method. The amount of carbon dioxide is equivalent to the sum of the glutamine and the glutamic acid, while the amount of ammonia corresponds to the glutamine alone. The content of glutamic acid is then calculated as the difference between these two values.

In a previous paper MUNKVAD has stated the experimental error as follows: For glutamic acid + glutamine the standard deviation in a single determination is 0.27 mg per cent, for glutamine 0.21 mg per cent, and for glutamic acid 0.36 mg per cent. In the tables of the present paper we have given only one decimal, as the second would be of no importance.

Case Material

All the children have been hospitalized, and the blood samples (25 ml of heparinized blood) were drawn in the morning before breakfast. Single determinations only have been carried out, as it was considered unwise to draw larger blood samples from the children.

The children with brain disorders were examined by ophthalmoscopy, skull radiography, and electroencephalography (except 3 children who could not cooperate), in addition to the routine clinical examination. In this group were 14 cases of cerebral palsy of the spastic type. Some of these were mentally retarded, and some had had convulsions. The electroencephalograms are mentioned in Table 3. Four of the remaining cases were epileptics.

UNIVERSITY OF MICHIGAN LIBRARIES

TABLE 1

Variations of plasma glutamine and glutamic acid in two children, one without brain disorder, and one with cerebral palsy and convulsions.

Date	K.H., ♀, yrs. Megacolon		H.A., ♀, 10 yrs. Cerebral palsy, convulsions	
	Glutamine mg per cent	Glutamic acid mg per cent	Glutamine mg per cent	Glutamic acid mg per cent
March 3	6.92	1.41		
April 30	6.48	4.14	9.46	0.00
May 4	9.56	0.00	6.06	1.74
„ 7	7.62	0.00	4.02	4.54
„ 11	7.71	2.45	6.57	3.86
„ 15	5.56	2.80	7.12	3.50
„ 18			9.37	0.00
„ 21	7.52	1.48	6.62	2.16
„ 28	6.83	2.87	5.87	2.49
Average	7.28	1.89	6.89	2.29

TABLE 2

Plasma glutamine and glutamic acid in 12 children without cerebral disorders.

Age years	Clinical diagnosis	Glutamine mg per cent	Glutamic acid mg per cent
C.J. ♂ 9	Malrotation of intestine	6.6	0.3
		5.0	2.5
F.C. ♂ 11	Inversion of testis	6.3	0.5
O.C. ♂ 10	Hernia, hydrocele	6.5	2.5
G.J. ♂ 5	Undescended testis	7.2	0.6
K.H. ♀ 5	Megacolon	7.3[1]	1.9[1]
I.V. ♀ 12	Asthma	6.0	1.3
I.L. ♀ 11	Asthma	8.7	1.0
S.P. ♂ 10	Undescended testis	7.5	3.4
J.L. ♂ 8	Small ventricular defect	5.5	0.3
H.T. ♂ 8	Insufficient anal sphincter	6.3	2.9
S.I. ♂ 13	Colitis	6.5	1.5
F.J. ♂ 6	Foreign body in intestine	6.7	0.0
	Average	7.9	1.7

[1] Average of 8 determinations.

TABLE 3

Plasma glutamine and glutamic acid in 25 children with cerebral disorders.

Age years	Clinical diagnosis	Electro-encephalo-gram	Glutamine mg per cent	Glutamic acid mg per cent
I.P. ♀ 8	Cerebral palsy	abnormal	6.7	0.8
E.B. ♀ 8	„ „ , seq. of encephalitis	normal	3.4	0.0
			5.8	0.2
C.H. ♀ 11	„ „ , convulsions	„	7.4	1.6
S.H. ♂ 6	„ „	„	7.2	3.7
E.I. ♂ 3	„ „	„	5.3	1.2
L.O. ♀ 8	„ „	abnormal	7.7	0.0
I.H. ♀ 7	„ „	not done	8.0	0.0
G.J. ♀ 9	„ „ , convulsions	abnormal	6.6	1.2
L.R. ♀ 5	„ „	„	4.6	0.0
S.M. ♂ 11	„ „	„	5.0	2.0
F.D. ♂ 7	„ „ , progressive	normal	3.8	1.0
H.A. ♀ 10	„ „ , convulsions	„	6.9[1]	2.3[1]
E.T. ♀ 6	„ „ , deafness	„	7.9	0.9
L.R. ♀ 1	„ „	not done	6.7	0.6
H.N. ♂ 3	Brain atrophy, petit mal	abnormal	2.8	0.1
P.H. ♂ 9	„ „ , oligophrenia	„	6.7	0.6
F.T. ♂ 8	Petit mal	„	8.1	2.9
M.H. ♀ 7	„ „	„	6.7	3.1
K.J. ♂ 1	Grand mal	„	7.0	0.0
L.R. ♀ 6	„ „ , familial	„	5.9	1.8
K.C. ♂ 9	Kataplexia	suspect	3.3	3.4
P.F. ♂ 2	Oligophrenia?	„	5.3	1.0
B.M. ♀ 7	Seq. of subdural hygroma	„	5.2	2.8
H.N. ♂ 8	Convulsions of Jackson type	abnormal	4.4	1.9
H.C. ♀ 9	Hydrocephalus	„	5.9	0.9
		Average	6.1	1.6

[1] Average of 8 determinations.

The children without brain disease, used as controls, were such patients as were admitted on account of hernia, undescended testes, and other non-neurological diseases (Table 2). These children were not examined by electro-encephalography or other special tests.

We have placed 5 neurotic children in a separate group, as abnormal levels of plasma glutamine and glutamic acid have been reported in psychotic patients, as mentioned before.

UNIVERSITY OF MICHIGAN LIBRARIES

TABLE 4

Plasma glutamine and glutamic acid in 5 neurotic children.

Age years	Clinical diagnosis	Electro-encephalo-gram	Glutamine mg per cent	Glutamic acid mg per cent
F.S. ♂ 5	Enuresis, obesity	normal	6.3	0.0
			6.0	2.6
C.C. ♂ 11	Tics	,,	5.6	1.4
A.C. ♀ 12	Psychogenic abd. pain	not done	7.1	1.7
E.N. ♂ 9	Neurosis, enuresis	normal	3.9	3.4
P.J. ♂ 12	Tics	,,	6.8	2.8
		Average	5.9	2.0

Results

First we have studied how much the plasma glutamine and glutamic acid may vary in the same individual at different times. It is evident that the ideal thing would be to determine the variations during a 24-hour period in a child, but this would require too large a quantity of blood. Instead of that we have made several determinations with a few days' interval in two children, one without brain disorder, and one with cerebral palsy and convulsions. All the blood samples were drawn in the morning before breakfast. It appears from Table 1 that very great variations occur. On some occasions even a glutamic acid concentration of zero was found. As mentioned before, this value is calculated as the difference between (1) glutamic acid + glutamine, and (2) glutamine. Owing to experimental error, this difference may become zero or even negative, in which case we have called it zero. Probably the glutamic acid concentration in these cases is not actually zero but only very low. Owing to our correction the calculated average of the glutamic acid concentrations is probably a little too high.

Table 2 shows the values obtained in the children without brain disorders. The variations from case to case are of the same order of magnitude as the variations seen in a single patient at different times, as shown in Table 1.

In children with brain disorders (Table 3) the variations of both the glutamine and the glutamic acid levels are as great as in the previous two tables. The glutamic acid level is equal to that in Table 2, but the glutamine level is lower, and this difference is statistically significant ($P < 0.01$). However, further studies are required to demonstrate that this difference is really due to the brain disorder and not to other factors, such as decreased muscular activity, etc.

The results from the neurotic children (Table 4) are too few to permit of any conclusions.

As the concentration of these substances varies so much in the same individual at different times, from as yet unknown reasons, it is evident that a determination of these values is of no diagnostic value.

Summary

With the method of KREBS, the plasma glutamine and glutamic acid have been determined in 12 children without cerebral disorders, and in 25 children with cerebral diseases, particularly cerebral palsy and epilepsy, and also in 5 children with neuroses. Very great variations occur in the same individual at different times. The children with cerebral disorders show the same glutamic acid level as the controls, but their glutamine level was lower. However, the method is of no diagnostic value. Further studies in this field will be carried out.

Taux de glutamine plasmatique et d'acide glutamique chez des enfants atteints de lésions cérébrales, par rapport aux enfants normaux.

Les taux de glutamine plasmatique et d'acide glutamique ont été étudiés par la méthode de Krebs chez 12 enfants normaux, 25 enfants atteints d'affections cérébrales (notamment des paralysies cérébrales et des épilepsies) et 5 enfants présentant des affections neurologiques. On a trouvé de grandes variations chez un même individu, selon le moment du prélèvement. Les enfants présentant des troubles cérébraux avaient un même taux d'acide glutamique que les témoins, mais un taux de glutamine diminué. Néanmoins, cette méthode semble sans valeur diagnostique. De nouvelles recherches dans ce domaine seront poursuivies.

Plasmaglutamin und Glutaminsäure bei Kindern mit Gehirnerkrankungen verglichen mit normalen Kindern.

Die Bestimmung der Plasmaglutamine und Glutaminsäure wurde nach der Methode von Krebs durchgeführt. Das Material bestand aus 12 Kindern ohne cerebrale Störungen und 25 Kindern mit cerebralen Erkrankungen, besonders cerebrale Kinderlähmung und Epilepsie, und außerdem 5 Kindern mit Neurosen. Sehr große Variationen treten beim gleichen Individuum zu verschiedenen Zeitpunkten auf. Kinder mit cerebralen Störungen haben dieselben Glutaminsäurewerte wie die Kontrollkinder, aber die Glutaminwerte sind niedriger. Die Methode ist jedoch nicht von diagnostischer Bedeutung und weitere Untersuchungen auf diesem Gebiet sollen durchgeführt werden.

Glutamina y ácido glutámico en el plasma de niños con enfermedades cerebrales. Comparación con niños normales.

Utilizando el método de Krebs se determinaron los niveles de glutamina y ácido glutámico en el plasma de 25 niños que padecían de diversas enfermedades cerebrales, especialmente parálisis cerebral y epilepsia, en 5 niños con neurosis y en 12 niños que no sufrían de afecciones cerebrales. En el mismo individuo pueden observarse de

tiempo en tiempo grandes variaciones en estos niveles. La concentración de ácido glutámico en el plasma de niños con enfermedades cerebrales es igual a la de los controles, pero el nivel de glutamina es menor. Sin embargo el método carece de valor diagnóstico. Se proseguirán las investigaciones en este terreno.

References

KREBS, H. A.: Quantitative determination of glutamine and glutamic acid. Biochem. J. *43:* 51, 1948.

MUNKVAD, I.: Glutaminsyre- og glutaminbestemmelser i plasma paa et psykiatrisk patientmateriale. Dissertation. Arne Frost-Hansens Forlag, Copenhagen 1951.

PRICE, J. C., WAELSCH, H. and PUTNAM, T.: *dl*-glutamic acid in the treatment of petit mal and psychomotor seizures. J.A.M.A. *122:* 1153, 1943.

WAELSCH, H.: Glutamic acid and cerebral function. Advances Protein Chemistry *6:* 299, 1951.

WEIL-MALHERBE, H.: The metabolism of glutamic acid in brain. Biochem. J. *30:* 665, 1936.

ZIMMERMANN, F. T. and BURGEMEISTER, B. B.: Permanency of glutamic acid treatment. Arch. Neurol. & Psychiat. *65:* 291, 1951.

Received 5.10. 1953.

Pediatric Department
Rigshospitalet
Copenhagen.

Acta Paediatrica **43**: 327—336. July 1954

From the Pediatric Clinic of Karolinska Sjukhuset, Stockholm (Head: Prof. A. Wallgren), and the Department of Ophthalmology, Sabbatsbergs Sjukhus, Stockholm (Head: I. Kugelberg M.D.)

Appearance of the Fundus Oculi in Prematurely Born Infants

Treated With and Without Oxygen

by A. HUGGERT

Introduction

The findings on examination of the fundus oculi in 130 prematurely born infants, especially with regard to the occurrence of the early stages of retrolental fibroplasia, and the probable relationship between these changes and the supply of oxygen to the children, have been reported in previous papers (HUGGERT 1952 and 1953). Since grave suspicions have arisen in many quarters that exposure to oxygen can affect the children detrimentally, it has been tried to avoid the use of oxygen to the greatest possible extent in the Pediatric Clinic. In this way it has been possible, at the same time, to provide a control group of 53 cases who have, in the main, not been treated with oxygen and who have been investigated ophthalmologically, in the same way as in the earlier material. The ophthalmological examinations have been directed especially towards ascertaining whether any difference could possibly be seen in the appearance of the fundus oculi in the children exposed to oxygen as against those not exposed. That the frequency of acute, as well as of clinically definite cicatricial retrolental fibroplasia decreases if oxygen is used more restrictedly, is evident from experiences in England (JEFFERSON) and Denmark (BRÆNDSTRUP and WINGE FLENSBORG), while there are contradictory statements from the U.S.A. (SZEWCZYK, diminished frequency; REESE and BLODI, no effect).

Case Material

Before discussing more fully the findings from examination of the fundus oculi in both groups, some words ought to be said concerning both the composition of the material and its comparability with regard to the proposed enquiry. The earlier larger series, as mentioned before, comprised 130 cases of which 9 died rather soon after birth. The remaining 121 cases, hereinafter termed group 1, had an average birth weight of 2050 g with 36 of them weighing 1800 g or under, while 5 weighed 1300 g or less. Of the 121 cases, 41 with an average birth weight of 1550 g had received about

45 % oxygen, for at least 14 days: the others, oxygen for a shorter period, or not at all. The smaller control group of 53 cases exhibited 5 deaths rather soon after birth and there were 4 cases who, because of threatening asphyxia, received oxygen for more than 14 days. Deducting these 9 cases, leaves the 44 who made up group 2. Of these 44, 3 had received oxygen for about a week and the remainder not at all, or only for 1—2 days, immediately after birth. The average birth weight was 1850 g and 21 of the cases weighed 1800 g or under, 2 of them 1300 g or less. A comparison between group 1 and group 2, as regards birth weight, indicates therefore that group 2, on account of its lower average birth weight, ought to be most likely to display retrolental fibroplasia and similar changes in the eye.

The children in both series have been investigated in the same way as mentioned previously—once weekly during a visit to the Pediatric Clinic, after which in group 1 only those children with a birth weight of under 1800 g were examined as a control measure at further intervals, up to six months of age. At the time for this comparison, all the children in group 1 were more than 1 year old and 28 in group 2 older than six months, with none of the remaining 16 in the latter series younger than 3 months. In all cases in group 2 where, after the hospital visits, a follow up examination was not done, the parents were contacted and asked about the condition of the children with special regard to the condition of the eyes, and all children with the slightest eye trouble were called in for investigation. It has not been possible to obtain information concerning 6 of the 48 children still living. Of these 6, 2 have been observed up to at least 2 months of age, without any pathological changes being seen in the eyes, and of the remaining 4, 2 weighed over 2000 g at birth. Only the remaining 2, with an observation period of from 4—6 weeks and a birth weight of 1760 and 1840 g respectively, might therefore have been likely to have developed a retrolental fibroplasia later. The youngest of these, at the time of the compilation of this group, was 9 months old. Since nowadays in Sweden there

TABLE 1

Relation between birth weight and fundus changes in both groups. Retrolental fibroplasia (R.f.), active phase = stages II–IV according to the author's classification (1952) or stages II–IV according to the classification given by the National Society for the Prevention of Blindness (Am. J. Ophth. *36*: 1333, 1953).

Birth weight g	Group 1	Oxygen more than 14 days	R.f. active phase	R.f. cicatr. phase	Oxygen >14 d. R.f. cases	Group 2	Oxygen more than 14 days	R.f. active phase	R.f. cicatr. phase
≤1,000	—		—	—	—	1	(1)	—	—
≤1,250	3	3	—	—		—	(1)	—	—
≤1,500	13	13	4	1	5	6	(1)	—	—
≤1,750	18	14	7	1	7	9	(1)	2+(1)	—
≤2,000	35	8	9	—	1	11	—	2	—
≤2,250	30	3	8	—	1	15	—	—	—
>2,250	22	—	3	—	—	2	—	—	—
	121	41	31	2	14	44	(4)	4+(1)	—

an obligation to notify cases of retrolental fibroplasia and nothing concerning these two cases has been reported, and since, moreover, neither showed any abnormality at the last ophthalmological examination, the possibility of a later development of retrolental fibroplasia may be excluded.

Results of Examination

Fully developed cicatricial retrolental fibroplasia has appeared in only 2 cases, both belonging to that part of group 1 which had received oxygen for a long time (both cases are more fully described in a previous communication, HUGGERT 1953). In group 2 no cases of cicatricial retrolental fibroplasia have been discovered. Widening of the retinal vessels, newly formed vessels together with oedematous changes of a more pronounced type in the periphery of the fundus oculi, all changes which resemble the acute stages of retrolental fibroplasia, have been recognised in 33 cases of the 121 in group 1, together with 4 cases of the 44 in group 2. Those cases have not been included in which a yellowish white reflex in the periphery of the fundus and very slight oedematous changes were seen, such as were reported earlier in about $^2/_3$ of all the cases in group 1. Of the 44 cases of group 2, these slight changes were seen in 12 cases, and oedema in 16 cases in all, i.e. in about $^1/_3$ of the cases.

As was pointed out in a previous communication, there seems to exist a definite connection between oxygen administration, and the more pronounced vessel changes, with marked oedema or actual retinal detachment. The results from group 2 where oxygen was used to a very small extent, seem to point in the same direction. Whether the very slight changes in the peripheral yellowish white reflex with only negligible oedema would appear relatively independently of oxygen administration, was discussed in a previous paper, in which it was my latest opinion that such slight changes occur without demonstrable relationship to oxygen. That such slight changes were seen to a lesser extent in group 2 than in group 1, is no certain confirmation of their having any connection with the administration of oxygen, since the definition of what is supposed to be a completely normal fundus is very uncertain in such cases. Possibly changes of this sort occur more often after exposure to oxygen than otherwise, but they are obviously relatively common also in cases which have not received oxygen. RYAN, likewise, calls attention to the fact that no definite connection between such changes and oxygen administration can be proved. It may be added that of the 4 cases which were excluded from group 2, because of having been exposed to oxygen for a longer period than 7 days, 2 showed slight vessel widening and oedematous changes, and 2 exhibited more pronounced changes of the same kind.

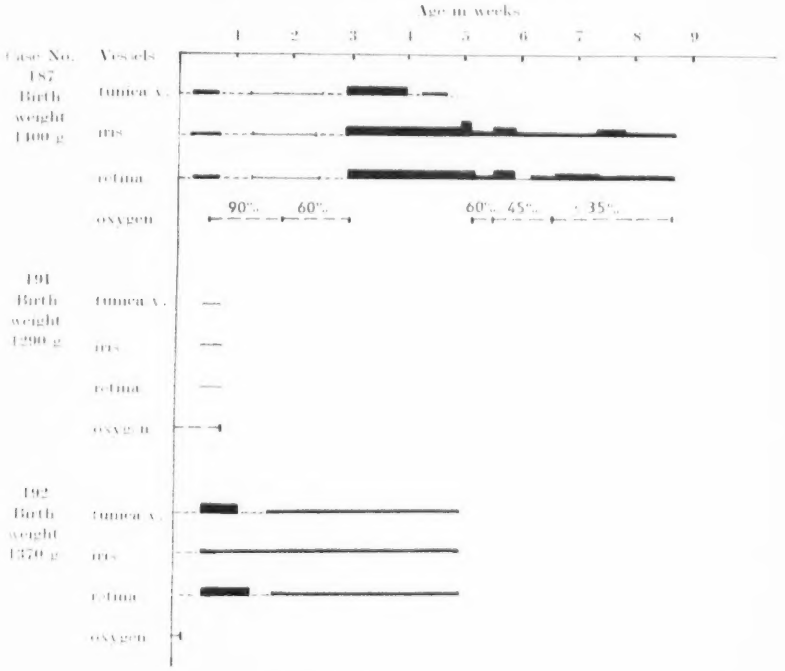
In the previous paper 27 cases were reported, in which, on some occasion,

extremely narrow retinal vessels were found. All these cases exhibited a vascular change in relation to continuous oxygen administration and it was therefore supposed to be the cause of the diminished calibre of the vessels. At the same time relatively pale fundi and papillae were found. In group 2 similar but not so markedly pronounced changes have been observed in 6 cases and in all of these the changes occurred during, or immediately after, exposure to oxygen. Of these 6 cases, 4 are those excluded from group 2 because of having received oxygen for more than 14 days. Of the other two, one was a child with a birth weight of 1000 g who received oxygen for 6 days and who, for a long time afterwards, showed relatively pale fundi and narrow vessels. The other case, with a birth weight of 1730 g, received oxygen for 5 days and showed narrow vessels during this time only. The fundal findings from this new series therefore verify the opinion which was formed from the earlier series and which is in agreement with what, among others, SZEWCZYK found, viz., that extremely narrow vessels are directly related to oxygen administration. This possibility involves a reservation in the case of children with very low birth weights and low blood values, in whom narrow vessels may possibly be seen without any relationship to continuous oxygen exposure. Among children with a birth weight of over 1300 g in my material, the difference in the appearance of the fundus with and without exposure to oxygen has been obvious. This is, perhaps, best illustrated in Table 2, which shows the appearance of the vessels in the eye at different times, in two children with birth weights of 1400 g who were, at the same time, being treated in the Clinic. One of the children received oxygen because of asphyxia, and the other none. These children are not included in group 2 since they were born after this paper was completed.

In this connection the question arises whether or not other blood vessels in the eye and vessels elsewhere in the body react in the same way. RUBINSTEIN has brought forward the hypothesis that a rapid rebuilding of the fetal blood vessels in the eye might be the cause of retrolental fibroplasia. A certain amount of support for this theory is derived from ZETTERSTRÖM's investigations concerning the closure of the ductus Botalli. He found that the lumen of the ductus Botalli closed more quickly in cases where oxygen was administered. To prove this theory further, I have in my own series undertaken an investigation on the rebuilding of the vessels in the tunica vasculosa in the cases in which these were relatively easily seen. Altogether in the whole series of 169 children (the 14 dead excluded), 26 showed distinct vessels which could be followed in repeated examinations. Of these 26 cases, 15 received oxygen for a longer time and 11 for a shorter, or not at all. No difference between both the groups, as regards the time during which the vessels could be seen, was forthcoming, and the cases are divided fairly evenly within the

TABLE 2

The connection between the supply of oxygen and the vessel calibre in the tunica vasculosa, iris and retina. Calibre of vessel: ——— wide, ——— normal, ——— narrow, ——— unknown. Cases 191 and 192 are uni-ovular twins, Case 191 who received oxygen during the whole time died after 5 days, showing multiple malformations. Case 187 developed a cicatricial retrolental fibroplasia, and the vessels of the fundus could not be examined after the 9th week.



time limits of 1—6 weeks after birth (5 of the 7 cases in which the vessels could be seen for three weeks or longer, belong to the oxygen group). It was, however, obvious that the vessels in the iris, as well as in the tunica vasculosa, were very narrow during oxygen administration and wide in its absence, and that with the withdrawal of oxygen there appeared a marked widening of the vessels of the iris, as well as of the vessel net in the tunica vasculosa (see Table 2).

Previously a large number of cases were shown from group I who on some occasion, and sometimes immediately after birth, or on stoppage of the supply of oxygen, showed extremely wide vessels both in the iris and the retina and in later cases, often without obvious oedema. This was interpreted as a reaction to the changes in oxygen tension, with the reservation that the connection was not so obvious, as it was regarding the occurrence of extremely

narrow vessels. Corresponding investigations on group 2 show that 24 of 4 cases (only the 5 dead excluded) on some occasion showed wide vessels i the retina and often at the same time in the iris. In the 4 cases which receive oxygen for more than 14 days, this widening of the vessels appeared in as sociation with the cessation of oxygen administration. Of the remaining 2 cases, 14 showed widening of the vessels immediately after birth, or withi the first week of life and often a distinct widening of the vessels in the iris, with a red brown color of the iris: while 6 showed the changes first afte about 14 days, during which period they had earlier shown a normal funda picture.

In one portion of these cases with late appearance of vessel widening, it has been possible to establish that they appeared in association with a dete rioration in the general condition. In this connection, it should be pointed out that a portion of the cases described earlier, with pronounced retinal oedema, showed this in association with digestive upsets, bronchial infections or other infective conditions having a general effect. That infections, especially of the bronchial type, play a definite part in the appearance of retrolental fibroplasia, is pointed out by CAMPBELL and SZEWCZYK and it is plainly evident from the case histories of certain writers (see for example RYAN, and BROWN and CORNER). Not only infective conditions, however, are contributory to the appearance of the early stages of retrolental fibroplasia. In my own series, pronounced changes with marked retinal oedema have been seen in a case of morbus haemorrhagicus with thrombocytopenia and Kernicterus, together with a markedly affected general condition, and in one case of suspected intracranial haemorrhage with pronounced asphyxia. In the former case relatively large retinal haemorrhages occurred in addition. This case belongs to the group which died relatively soon after birth. The latter case survived and the retinal changes resolved completely.

Discussion

A comparison between the two groups indicates the following. The appear ance of very narrow vessels in the retina, iris and tunica vasculosa togethe with pale papillae, appear to have a direct relationship to the supply o oxygen. Wide vessels and oedematous changes in the retina, similar to th early stages of retrolental fibroplasia, may occur immediately after birth, o in association with the cessation of the supply of oxygen. These changes ca also occur in association with other conditions—especially, it seems, in as sociation with infectious diseases and others with a marked effect on th general condition. An absolute or relative anoxia may be the deciding facto in these cases. If it can be demonstrated that supplying oxygen, during a lon

period, either directly or indirectly, gives rise to retrolental fibroplasia, then surely it should be avoided, so far as is possible: but even if only grave suspicions are held, in deference to the present viewpoint, one should act accordingly. The comparison between these certainly relatively small series would also seem to show that unless there is, by not giving oxygen, a greater risk of increased mortality, or of the onset of complications, oxygen should be avoided in most cases.

With reference to the mortality in the group which received oxygen more restrictedly, it should be mentioned that of the 5 dead infants, 3 had received oxygen during the whole of their lifetime, and 2 on isolated occasions only. In order not to give a false idea of the mortality among the prematures during the time the cases of group 2 were being accumulated, it may be stated that during this period, 16 more prematures were cared for in the department. Since these lived some few days only, they were not subjected to an ophthalmological examination. All 16 cases had from birth, and for the whole of their life time, received oxygen because of pronounced asphyxia. Only in the two cases mentioned who received oxygen on isolated occasions only, might one think that a more liberal supply of oxygen would have altered the mortality figures. One of these is the aforementioned case with morbus haemorrhagicus and thrombocytopenia, and the other is a child with a birth weight of 2050 g, who 4 days after birth died as a result of marked atelectasis of the lungs and oedema of the brain. In this latter case, oxygen was used first when the child, after having previously been in good general condition, suddenly became asphyctic. Because of the relatively high birth weight, the treatment would have been the same, even if ample oxygen had been supplied more liberally as in group 1. Neither of these two cases should reasonably be considered to show that the regimen of treatment which was carried out in group 2 would have produced a worse result than that which was used in group 1.

Conclusion

Since, as stated, the series is small, no far-reaching conclusions can be drawn from it; but according to the author's opinion, one should in the great majority of cases be able to dispense with oxygen and only resort to it in pronounced asphyxia. If oxygen is withdrawn it should be done gradually and not rapidly. On withdrawal of oxygen the fundus should be examined repeatedly and if there is any tendency towards the development of wide retinal vessels and oedema, this is best treated by putting the child back into the oxygen milieu, occasionally. As pointed out first by SZEWCZYK and later confirmed elsewhere (see, among others, JEFFERSON, SWART *et al.*, TUGGERT) by this means the fundal changes often disappear. Occasional

supply of oxygen ought also to be given to children who contract infective conditions of any sort, or who for any other reason show a deterioration in the general condition. In the main, the same indications and instructions for giving oxygen which have been listed here, have been recommended by other investigators (VON WINNING, BRÆNDSTRUP and WINGE FLENSBORG, CROSSE and EVANS, SZEWCZYK, PATZ *et al.*).

As the author has pointed out previously, these procedures are imperative until one succeeds in demonstrating that oxygen as such, or the relative anoxia following administration of oxygen, really acts detrimentally, or, on the other hand, succeeds in acquitting oxygen completely of being a cause of retrolental fibroplasia.

The experimental investigations of the last two years seem rather to have shown incontrovertibly that high concentrations of oxygen, as well as rapid changes from high to low oxygen tensions, do cause the obvious acute stages of retrolental fibroplasia in mammalian newborn (GYLLENSTEN and HELLSTRÖM, ASHTON and co-workers, PATZ and co-workers).

Summary

The author has compared a group of 121 prematurely born children (5 with a birth weight at the highest 1300 g) who received a large supply of oxygen, with another group of 44 prematures (2 with a birth weight at the highest 1300 g) who received oxygen to a very slight extent. In the first group, 2 cases of cicatricial retrolental fibroplasia developed, in the latter group none, while acute peripheral retinal changes of a more pronounced degree occurred among 33 and 4 children, respectively. No definite increase in mortality could be proved to occur among the children as a result of the more restricted use of oxygen.

Very narrow vessels in different parts of the eye, together with pale papillae, were seen during the continuous use of oxygen, while dilated vessels and oedema of the fundus oculi certainly occurred more often in children who received oxygen, but these changes did occur also in other cases. In those cases dilated vessels were often seen immediately after birth, or in relation to a lowered general condition, especially if associated with infections.

Oxygen administration is only to be recommended in cases of pronounced asphyxia: at the same time, the importance of a gradual withdrawal of oxygen and control examination of the fundus oculi is stressed in these cases.

Aspect du fond d'œil chez les prématurés ayant ou n'ayant pas reçu d'oxygène.

L'auteur a comparé deux groupes de prématurés : L'un de 121 (dont 5 pesant moins de 1300 g à la naissance) qui avait reçu un apport d'oxygène très large, et un autre groupe de 44 prématurés (dont 2 pesaient moins de 1300 g à la naissance) qui

avait reçu un faible apport oxygéné. Dans le premier groupe, on a rélevé deux cas de fibroplasie rétrolentale, et aucun dans le deuxième groupe. Des altérations rétiniennes périphériques survenaient chez 33 et 4 prématurés respectivement. L'usage plus restreint de l'oxygène dans le second groupe n'a pas modifié le taux de la mortalité. On observait par l'usage continu de l'oxygène une papille pâle, et de vaisseaux très étroits. Une dilatation des vaisseaux et l'œdème du fond d'œil survenait certainement plus fréquent chez les enfants recevant de l'oxygène; mais ces modifications s'observent également dans les autres cas. Une dilatation des vaisseaux peut se voir immédiatement après la naissance, et aussi en rapport avec une baisse de l'état général, surtout en cas d'infection associée. L'administration d'oxygène n'est à recommander que dans les cas d'asphyxie : A noter l'importance dans ces conditions d'une diminution aussi rapide que possible du taux de l'oxygène, et les examens du fond d'œil.

Das Bild des Fundus oculi bei Frühgeburten, die mit und ohne Sauerstoff behandelt wurden.

Der Verf. hat eine Gruppe von 121 Frühgeburten (5 hatten ein Geburtsgewicht bis zu 1300 g), die reichliche Sauerstoffzufuhr erhielt, mit einer anderen Gruppe von 44 Frühgeburten (2 hatten ein Geburtsgew. bis 1300 g) verglichen, die nur in sehr geringem Ausmasse Sauerstoff erhielten. In der ersten Gruppe traten 2 Fälle von retrolentaler Fibroplasie auf, in der zweiten Gruppe kein Fall, während Veränderungen in der peripheren Retina bei 33 bzw. 4 Kindern auftraten. Eine definitive Zunahme der Mortalität infolge der beschränkten Anwendung von Sauerstoff konnte nicht nachgewiesen werden. Bei langdauerndem Gebrauch von Sauerstoff sah man sehr enge Gefässe in den verschiedenen Teilen des Auges verbunden mit einer Abblassung der Papille, während erweiterte Gefässe und Ödem des Augenfundus sicherlich öfter bei Kindern auftraten, die Sauerstoff erhalten hatten; jedoch traten diese Veränderungen auch in anderen Fällen auf. Erweiterte Gefässe wurden auch oft sofort nach der Geburt beobachtet und in Beziehung zu einem verschlechterten Allgemeinzustand, besonders in Verbindung mit Infektionen. Sauerstoffzufuhr kann nur in Fällen von Asphyxie empfohlen werden, und in diesen Fällen ist es wichtig, das Aufhören der Sauerstoffzufuhr allmählich geschehen zu lassen und wiederholte Kontrolluntersuchungen des Augenhintergrundes durchzuführen.

Aspecto del fondo de ojo en niños prematuros, tratados con y sin oxígeno.

El autor ha comparado un grupo de 121 prematuros (5 con un peso de 1300 g o menos al nacer) que recibieron abundante oxígeno, con otro grupo de 44 prematuros (2 con peso igual o inferior a 1300 g)que recibieron oxígeno en forma muy restringida. En el primer grupo se desarrollaron dos casos de fibroplasia retrolenticular, en el segundo grupo ninguno; alteraciones retinianas periféricas de grado avanzado se presentaron en 33 y 4 niños respectivamente. No pudo demostrarse aumento en la mortalidad entre los prematuros que recibieron oxígeno en forma más restringida. Durante la administración continua de oxígeno las papilas se mostraban pálidas y se observaban vasos de calibre muy estrechado en diversas partes del ojo. Dilatación vascular y edema del fondo de ojo se presentaron con frecuencia indudablemente mayor en los niños que recibían oxígeno, pero también fueron observados en otros casos. A menudo se observaron vasos dilatados inmediatamente después del nacimiento y en relación con malas condiciones generales, especialmente cuando éstas estaban asocia-

das a infecciones. La administración de oxígeno solo debe recomendarse en casos d asfixia. También debe insistirse en estos casos en la importancia de una gradu disminución en el suministro de oxígeno y en el examen de control del fondo de oj

References

Ashton, N., Ward, B. and Serpell, G.: Role of oxygen in the genesis of retrolental fibroplasi Brit. J. Ophth. *37:* 513, 1953.

Brændstrup, P. and Winge Flensborg, E.: Retrolental fibroplasi. Ugesk. læger *115:* 317, 1953.

Brown, C. A. and Corner, Beryl: Retrolental fibroplasia. Brit. J. Ophth. *36:* 281, 1952.

Campbell, Kate: Intensive oxygen therapy as a possible cause of retrolental fibroplasia: a clinic approach. M. J. Australia *38:* 48, 1951.

Guy, L. P., Dancis, J. and Lanman, J. T.: Retrolental fibroplasia. Am. J. Ophth. *36:* 85, 1953.

Huggert, A.: The supply of oxygen to prematures and the appearance of retrolental fibroplasi Acta pædiat. *42:* 147, 1953.

Jefferson, E.: Retrolental fibroplasia. Arch. Dis. Childhood *27:* 329, 1952.

Patz, A., Eastham, Ann, Higginbotham, D. H. and Kleh, Th.: Oxygen studies in retrolental fibr plasia. Am. J. Ophth. *36:* 1511, 1953.

Reese, A. B. and Blodi, F. C.: Retrolental fibroplasia. New York J. Med. *52:* 2869, 1952.

Rubinstein, K.: Mechanism of retrolental fibroplasia. Brit. J. Ophth. *36:* 303, 1952.

Ryan, H.: Retrolental fibroplasia. Am. J. Ophth. *35:* 329, 1952.

Silverman, W. A., Blodi, F. C., Locke, J. C., Day, R. L. and Reese, A. B.: Incidence of retrolent fibroplasia in a New York nursery. Arch. Ophth. *48:* 698, 1952.

Swart, J. Th., van der Hoeven and Mak, Th. M. B.: Retrolentale fibroplasie en zuurstof. Maand schr. Kindergeneesk. *20:* 276, 1952.

Szewczyk, T. S.: Retrolental fibroplasia and related ocular diseases. Am. J. Ophth. *36:* 1336, 195

von Winning, C. H. O. M.: Nederlandse ervaringen over retrolentale fibroplasie. Maandschr. Kinder geneesk. *20:* 268, 1952.

Zetterström, R.: Personal communication.

For further references see Huggert 1953.

Received 6.11. 1953.

Department of Ophthalmology
Sabbatsbergs Sjukhus
Stockholm.

Acta Pædiatrica **43**: 337—341. July 1954

From the Institute of Biochemistry, University of Aarhus (Chief: Professor Fritz Schonheyder, M.D.), and the Pediatric Department of Aarhus University, Aarhus Kommunehospital (Chief: Professor Bent Andersen, M.D.)

Amino-Aciduria in Galactosaemia

by SV. DARLING and OLE MORTENSEN

Recently it has been demonstrated that urine from patients suffering from the rare metabolic disorder galactosaemia, contains pathological amounts of amino-acids. Thus, in 1952 HOLZEL, KOMROWER and WILSON reported two cases of galactosaemia associated with pathological amino-aciduria, and BICKEL and HICKMANS demonstrated amino-aciduria in two patients described by BRAY, ISAAC and WATKINS. Independently of these reports, we demonstrated abnormal amino-aciduria in an infant with typical galactosaemia; this case is reported below.

Case Record

A 5-month-old female infant was admitted to the University Pediatric Clinic, Aarhus Municipal Hospital, in the autumn of 1952. The patient presented typical symptoms of galactosaemia, malnutrition, mental retardation, cataracts, hepatomegaly, osteoporosis, dyspepsia, albuminuria, galactosaemia and galactosuria. The reducing substance from both blood and urine was identified, both chemically and by chromatography, as galactose. The galactose-tolerance test was abnormal. Urinary excretion of calcium and amino-acids was increased. The striking improvement after removal of milk from the diet and the recurrence of symptoms when the infant was again placed on a milk diet, confirmed the diagnosis. (The case report will be published in greater detail by SØNDERGAARD and MORTENSEN.)

Methods of Investigation

A derivative of the reducing substance in the urine was prepared by treating 50 ml of urine with 2.5 g of sodium acetate, 2.5 ml of glacial acetic acid and 4.5 ml of phenyl hydrazine. The mixture was heated on a boiling water bath for 30 minutes. Yellow crystals separated in copious amounts on cooling. After recrystallization from ethanol-water, this substance had a melting point of 182°C. A known sample of galactose osazone melted at 180°, and the mixed melting point of the two compounds was 182°. Thus, the reducing substance in the urine was identified as galactose. Microscopic examination of the osazones and one-dimensional paper chromatography of the untreated urine, confirmed this conclusion.

The presence of carbohydrates in urine and blood was shown by one-dimensional chromatography, using Whatman paper No. 1 and ethyl acetate-pyridine-water (8 : 4 : 2 v/v). The paper strip was irrigated for 20 hours. Aniline phosphate reagent served to detect the carbohydrates on the chromatogram.

Amino-acids in urine and blood were identified by two-dimensional chromatography, using Whatman paper No. 1. The chromatograms were carried out with methyl cellosolve (9 : 1 v/v) as the first solvent and phenol-water (75 : 25 w/v) as the second (ammonia was added to the phenol tank). In testing urine and blood for the presence of amino-acids, a constant amount of nitrogen was taken (250 γg). Prior to chromatography, the blood was deproteinized by adding four volumes of 96 per cent ethanol. After filtering off the precipitate, the filtrate was evaporated to dryness in a vacuum desiccator, over phosphorous pentoxide. The solid was dissolved in water.

Results

The urine was studied on numerous occasions by one-dimensional chromatography, while the infant was on a milk diet. All the samples showed abnormal excretion of amino-acids and galactose.

Two-dimensional chromatography of the urine revealed numerous amino-acids, some of them in considerable amounts, as appears from the diagram (Fig. 1). The urine was placed at the right-hand bottom corner. The methyl cellosolve solvent was run first (from below upwards), followed by phenol (from right to left). The spots are shown in their usual positions on an actual chromatogram. Large circles indicate that the amino-acids concerned were excreted in large amounts. After four days on a milk-free diet, the excretion became more normal (Fig. 2).

Later, when the infant was again placed on a milk diet, the excretion increased, resulting in a pattern similar to that of Fig. 1. On a lactose-free diet, the excretion again diminished within 24 hours.

When the infant had been on a milk-free diet for 8½ months, a renewed study of the urine showed excretion of alanine, glycine and serine in considerable amounts, glutamic acid and histidine in smaller quantities, and traces of alpha-aminobutyric acid.

The amino-acid content of the blood, which was independent of the presence or absence of milk in the diet, was assessed to be within normal limits.

Discussion

In the four cases previously reported, excretion of considerable amounts of amino-acids was observed. HOLZEL *et al.* found excretion of large quantities of serine, threonine, methyl histidine, lysine and tyrosine, on which C. H. DENT commented that "it could be that the pattern is specific for the disease". Whether this be the case, cannot as yet be decided on the basis of the few case records available. Serine, glycine and threonine were present in all

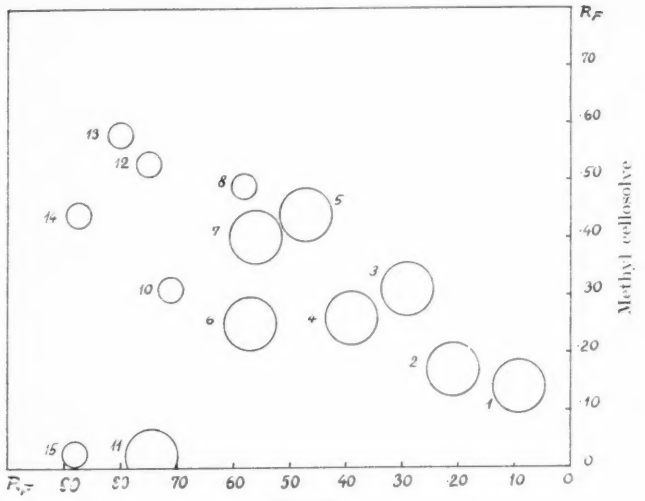


Fig. 1.

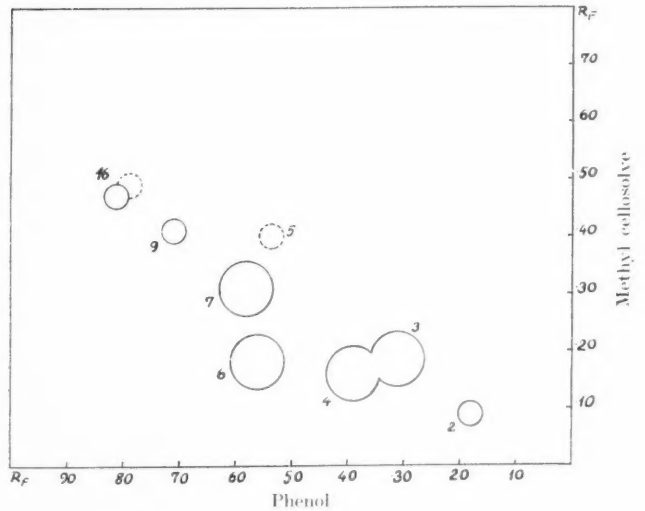


Fig. 2.

Fig. 1. Chromatogram of the urine while the infant was on a milk diet.
Fig. 2. Chromatogram of the urine after four days on a milk-free diet.

Identification of spots. 1, asparagine; 2, glutamic acid; 3, serine; 4, glycine; 5, threonine; 6, glutamine; 7, alanine; 8, tyrosine; 9, alpha-aminobutyric acid; 10, histidine, 11, lysine; 12, tryptophan; 13, valine; 14, proline; 15, arginine; 16, unidentified.

five patients, while cysteic acid, alanine, tyrosine, valine and lysine were observed only in four of the cases.

In one patient, KOMROWER (1953) found a normal content of amino nitrogen in the blood. As the amino-acid level of the blood was also normal in our patient, the pathogenesis cannot, as in liver disease, be explained by a simple "overflow" mechanism. It would be more reasonable to assume that the disorder is due to a true renal mechanism, as is known from the Fanconi syndrome and Wilson's disease.

It is known that amino-aciduria may occur in various intoxications produced by substances having a toxic effect on the kidneys, such as uranium, lead and lysol. It would be reasonable to assume that galactose also exerts a toxic effect on the kidneys, similar to that believed to be exerted on the liver, the central nervous system, and the lens of the eye.

The fact that BELL *et al.* (1950) observed fatty degeneration of the cells of the convoluted tubules in a patient with galactosaemia, lends support to the assumption that the renal tubules are damaged.

The increased urinary excretion of calcium, which was demonstrated in our patient, suggests that tubular resorption of amino-acids was not the only function impaired.

If the theory that albumin is normally excreted in the glomeruli and resorbed in the tubules be correct (see RATHER 1952), albuminuria in galactosaemia may also be taken as evidence in support of the assumption of impaired tubular function.

When the function of the proximal tubules is impaired, which might be presumed to be the case in galactosaemia, glycosuria might be expected. Its absence in galactosaemia might be explained by the low glucose level of the blood. In our patient transitory glycosuria (confirmed by chromatography) was observed when milk was omitted from the diet, whereas excretion of glucose was not demonstrated on any occasion, while the infant was on a milk diet.

As amino-aciduria diminishes when the patients are given a milk-free diet, the supposed renal changes must, at least partially, be reversible. However, BICKEL and HICKMANS made brief mention of a patient in whom amino-aciduria persisted, despite a milk-free diet. They did not state at what age this patient was treated.

Summary

A case of galactosaemia in a 5-month-old infant was studied by paper chromatography. The pronounced amino-aciduria which was present, diminished when the patient was placed on a milk-free diet. Amino-aciduria in galactosaemia is presumed to be of renal origin.

Aminoacidurie au cours de la galactosémie.

Un cas de galactosémie chez un nourrisson de 5 mois a été étudié par la chromatographie sur papier. L'importante aminoacidurie qu'on avait observée, diminuait lorsque le malade était soumis à un régime sans lait. Les auteurs pensent que l'aminoacidurie au cours de la galactosémie est d'origine rénale.

Aminoacidurie bei Galaktosämie.

Ein Fall von Galaktosämie bei einem 5 Monate alten Kind wurde mit Hilfe der Papierchromatographie studiert. Die ausgesprochene Aminoacidurie verschwand, nachdem der Patient eine milchfreie Diät erhielt. Man nimmt an, daß die Aminoacidurie bei Galaktosämie renalen Ursprungs ist.

Aminoaciduria en la galactosemia.

Un caso de galactosemia en un lactante de 5 meses de edad fué estudiado por cromatografía en papel. La marcada aminoaciduria que presentaba el paciente disminuyó al excluirse la leche de la dieta. Se presume que la aminoaciduria en la galactosemia es de origen renal.

References

Bell, L. S., Blair, W. C., Lindsay, S. and Watson, S. J.: Lesions of galactose diabetes. Pathologic observations. Arch. Path. *49:* 393, 1950.

Bender, A. E.: Methyl cellosolve as a developing solvent in paper partition chromatography. Biochem. J. *48:* XV, 1951.

Berke, H. and Rothstein, A.: Aminoaciduria in uranium poisoning. J. Pharmacol. & Exper. Ther. *96:* 198, 1949.

Bickel, H. and Hickmans, E. M.: Paper chromatographic investigations of the urine of patients R. T. and R. R. Arch. Dis. Childhood *27:* 348, 1952.

Bray, P. T., Isaac, R. J. and Watkins, A. G.: Galactosaemia. Arch. Dis. Childhood *27:* 341, 1952.

Bryson, I. L. and Mitchell, T. I.: Improved spraying reagents for the detection of sugars on paper chromatograms. Nature *167:* 864, 1951.

Holzel, A., Komrower, G. M. and Wilson, V. K.: Amino-aciduria in galactosaemia. Brit. M. J. *1:* 194, 1952.

Jermyn, M. A. and Isherwood, F. A.: Improved separation of sugars on the paper partition chromatogram. Biochem. J. *44:* 402, 1949.

Komrower, G. M.: L'Amino-acidurie dans la galactosémie. Arch. franç. pédiat. *10:* 185, 1953.

Mortensen, O. and Søndergaard, G.: To be published.

Rather, L. J.: Filtration, resorption and excretion of protein by the kidney. Medicine *31:* 357, 1952.

Spencer, A. G. and Franglen, G. T.: Gross amino-aciduria following a lysol burn. Lancet *262:* 190, 1952.

Wilson, W. K., Thomson, M. L. and Dent, C. E.: Amino-aciduria in lead poisoning. Lancet *265:* 66, 1953.

Received 7.12. 1953.

Institute of Biochemistry
University of Aarhus
Aarhus, Denmark.

Acta Paediatrica **43**: 342—346. July 1954

From the Clinical Chemical Laboratory of the Onze Lieve Vrouwe Gasthuis, Amsterdam (Head: Dr. Th. Strengers), the Pediatric Department of the Onze Lieve Vrouwe Gasthuis, Amsterdam (Head: Dr. G. A. Fehmers), and the Department of Obstetrics and Gynaecology of the Onze Lieve Vrouwe Gasthuis, Amsterdam (Head: Dr. H. Rottinghuis).

Plasma Electrolytes in the Neonatal Period

by TH. STRENGERS, JOHANNA W. MAAS, H. ROTTINGHUIS and G. A. FEHMERS

Introduction

In contrast to adults, the normal values for the plasma electrolytes in infants in their first few days of life have not been studied extensively and the data given by different investigators are to some degree contradictory.

It is generally agreed that the neonatus—and especially the premature infant—has a tendency to hyperchloraemic acidosis.

Reardon *et al.* (1950) found the following mean values in 73 premature infants, aged 1 to 65 days: plasma pH 7.31; CO_2 content 20.1 meq/L; Cl 111 meq/L and total base 159 meq/L. The corresponding values in 16 adolescent boys were 7.42, 23.9, 102 and 154. These investigators ascribe this slight, uncompensated acidosis to an anaerobic metabolism resulting from tissue anoxia. Since they found these values in premature infants before the first feeding, they conclude that the influence of food is only of secondary importance.

Darrow *et al.* (1945) showed, however, that the electrolyte composition of the plasma in premature infants can be influenced by food. On a diet of unmodified protein milk these infants developed severe acidosis with a rise of the Cl content and a drop of the pH and the Na and CO_2 concentrations. This they ascribe to an excess of Cl in the food, this Cl being excreted with difficulty and only in part together with Na.

Hoffman *et al.* (1948; 1949) extended these investigations and carried out balance studies on infants aged 6–38 days given a diet of protein milk or of evaporated milk. In 28 premature infants on the evaporated milk diet, they found the following mean values in blood from the internal jugular vein: Cl 111 ± 3; CO_2 18.4 ± 2.1; Na 141 ± 3; K 5.4 ± 0.4; PO_4 7.6 ± 1.0; Ca 5.6 ± 0.4 (all in meq/L); and total protein 5.20 g/L. (Their corresponding values for adults are Cl 104, Na 143, K 5.0, and CO_2 27.0.)

These infants, therefore, have a slight hyperchloraemic acidosis, which does not give rise to clinical manifestations. After a few months the values approach those found in adults.

The infants receiving a protein milk diet developed severe acidosis, which regressed rapidly after return to a diet of evaporated milk. The Cl content rose from 110 to 116, the Na dropped from 141 to 136, and the CO_2 from 18.8 to 12.0 meq/L. In 7

all-term infants aged 7–11 days these investigators found the same phenomena but to a much less pronounced degree.

As regards the potassium level, KOTIKOFF (1933) found a mean of 7.03 meq/L in 14 infants under one month of age; MCCANCE & YOUNG (1941) found 7.65 meq in 12 infants aged 7–14 days. SVENDSEN (1949) found in 9 premature and 5 full-term infants a mean K content of 16.3 and 18.9 mg per 100 ml respectively at the age of 7 days, and of 18.0 and 17.9 mg per 100 ml respectively between the ages of 2 and 8 weeks. EARLE *et al.* (1951) determined a mean of 5.0 meq/L in 9 samples of placental blood and a mean of 4.89 meq/L in 6 full-term infants aged 1–3 days and 9 aged 6–9 days. HOFFMAN *et al.* (loc. cit.) found a mean of 5.4 ± 0.4 meq/L in 28 premature infants aged 6–38 days. BRENNES & GROLHA (1953) found in the umbilical blood of 103 newborn a mean potassium content of 4.95 meq/L (range 3.82 to 5.67) and in 39 children aged 1–16 months, a mean of 4.96 meq/L.

Most of the above investigations either concerned older infants, or were based on analyses of umbilical blood, while the groups examined were heterogeneous with respect to age.

We therefore undertook the analysis of plasma electrolytes in premature and full-term infants on the first day of life and studied the changes in these values during the first week, in infants fed on human milk.

Methods

All determinations were carried out in heparinized plasma. A correction was made for the electrolyte content of the heparin used. The blood was obtained from a puncture in the heel and was collected under paraffin oil in a calibrated tube in which 1 ml heparin solution was evaporated (heparinum Vitrum). A special collection apparatus was constructed to prevent the blood from coming into contact with the air (STRENGERS & V. D. KOLK 1953).

The chloride was determined potentiometrically (STRENGERS & ASBERG 1953), Na and K were determined by flame photometry after deproteinization of the plasma with trichloracetic acid, using a Beckman-flame photometer (STRENGERS & KLINKENBERGH 1952). The CO_2 was determined by a micro-modification of the titrimetric method of van Slyke (STRENGERS & V. D. KOLK l.c.).

Results and Discussion

The mean electrolyte values in 32 full-term infants (> 2500 g) and 30 premature infants (1400–2500 g) are shown in Tables 1 and 2. (In view of the fact that not all determinations were carried out every day in every case, the number of determinations (n), from which the mean value was calculated, is stated.)

The figures show that the Na content in the plasma in the full-term infants on the first day did not differ from that in adults.

TABLE 1

Mean electrolyte contents (meq/L) for plasma in 32 full-term infants in the first week. (To make a comparison possible, the electrolyte values we found in the capillary blood of 25 adults are included.)

	n	1st day	*n*	2nd day	*n*	3rd day	*n*	5th day	*n*	7th day	*n*	Adults
Na . .	26	141 ± 4.1	5	138 ± 3.5	15	142 ± 6.0	11	143 ± 7.0	11	140 ± 6.0	25	140 ± 3.5
K . .	28	5.1 ± 0.49	5	4.9 ± 0.43	15	4.8 ± 0.50	11	4.8 ± 0.50	11	4.6 ± 0.3	25	4.8 ± 0.46
Cl . .	26	104 ± 4.8	6	104.6 ± 4.1	15	104.6 ± 7.3	11	104.8 ± 4.0	11	104 ± 5.0	25	105.3 ± 3.5
CO_2 . .	8	18.7 ± 0.73	6	20.4 ± 1.55	9	20.8 ± 1.22	9	20.5 ± 0.77	10	22.3 ± 1.47	25	23.10 ± 2.08

The potassium content was higher, as was found also by EARLE *et al.* in placental blood, but the difference is not significant. The chloride content was normal, but on the first day there was a significant decrease of the CO_2 content.

The small differences in this electrolyte pattern from that in adults disappeared gradually in the next few days and on the 7th day the pattern was absolutely identical with that in adults, except for a slight acidosis. The rapid decrease of the acidosis from the first day onward, suggests that this acidosis is the consequence of anaerobic metabolism in utero or during birth.

The premature infants also showed normal Na values but the K level was somewhat higher than that in the full-term infants and remained higher than that in adults, throughout the first week. These differences, however, are not significant.

Distinct differences are shown by the premature infants with respect to the anions. The low value of the CO_2 content was of a more lasting character than in the full-term infants. In contrast to the latter group, the premature infants showed hyperchloraemic acidosis, the chloride level remaining continuously elevated during the first week. In addition to the influence of anaerobic metabolism, the physiological incompleteness of development of the kidney and the resulting low Cl clearance must be held responsible for this hyperchloraemic acidosis. The conclusion is in agreement with the observations of HOFFMAN *et al.* (l.c.), who noted that on a diet high in Cl the premature infant in particular develops a severe hyperchloraemic acidosis in a short time.

Another striking feature is the large measure of dispersion of all the values for premature infants. In order to ascertain whether this is a sign that premature infants are especially labile with regard to the maintenance of their electrolyte balance, we calculated the mean of the values and the standard

TABLE 2

Mean electrolyte contents (meq/L) for plasma in 30 premature infants in the first week.

	n	1st day	*n*	2nd day	*n*	3rd day	*n*	5th day	*n*	7th day	*n*	Adults
Na	30	139 ± 7.8	13	138 ± 7.4	12	138 ± 12.0	10	141 ± 11.0	7	139 ± 3.5	25	140 ± 3.5
K	30	5.2 ± 0.6	13	5.0 ± 0.7	12	5.0 ± 0.6	10	4.9 ± 0.5	7	5.1 ± 0.3	25	4.8 ± 0.40
Cl	22	110.9 ± 5.9	13	109 ± 7.0	12	111 ± 8.7	10	111 ± 7.7	7	112 ± 3.4	25	105.3 ± 3.5
CO_2	5	16.4 ± 2.26	3	17	7	20.3 ± 2.92	9	18.8 ± 2.23	9	19.3 ± 2.60	25	23.10 ± 2.08

deviation for the individual infants whose electrolyte values had been determined on 5 or more days.

From these calculations, too, it was evident that the dispersion of the values, with the exception of that for the CO_2 content, is greater in premature than in full-term infants.

Summary

1. The plasma Na, K, Cl and CO_2 levels were determined in 32 full-term and 30 premature infants, from the 1st to the 7th day inclusive.

2. The full-term infants showed on the first day a slight acidosis which disappeared gradually in a few days. The other values were the same as in adults.

3. The premature infants showed a normal Na and a slightly high K content, but they had a distinct hyperchloraemic acidosis, which remained stationary during the first week.

4. The acidosis on the first day is ascribed to residual effects of an anaerobic metabolism in utero or during birth. The hyperchloraemic acidosis of the premature infants is ascribed to the physiological immaturity of the kidney with respect to the chloride clearance.

5. The electrolyte values in premature infants showed a large dispersion, which points to the lability of the premature infant in maintaining the equilibrium of plasma electrolytes.

Les électrolytes du plasma chez le nouveau-né.

Les taux plasmatiques du Na, K, Cl et CO_2 ont été étudiés chez 32 enfants nés à terme, et chez 30 prématurés, du 1er au 7^{me} jour, après la naissance. Chez les enfants à terme, on observait le premier jour une discrète acidose, disparaissant progressivement les jours suivants. Les taux des autres substances étaient identiques à ceux de l'adulte. Chez les prématurés, on notait une natriémie normale, mais une kaliémie légèrement élevée, ainsi qu'une nette acidose hyperchlorémique, demeurant identique au cours de la première semaine. L'acidose du premier jour est interprétée comme une manifestation résiduelle du métabolisme anaérobie existant in utero, et à la naissance. L'acidose hyperchlorémique des prématurés est interprétée comme une immaturation physiologique du rein, modifiant la clearance des chlorures. Les taux d'électrolytes du prématuré révélaient une grande variabilité, témoignant de la difficulté pour celui-ci de maintenir un équilibre correct des électrolytes du plasma.

Plasmaelektrolyte in der Neugeborenenperiode.

Der Gehalt des Plasmas an Na, K, Cl und CO_2 wurde bei 32 ausgetragenen Kindern und 30 Frühgeburten vom 1. bis zum 7. Lebenstage einschließlich bestimmt. Die ausgetragenen Kinder zeigten am ersten Tage eine leichte Azidose, die in wenigen Tagen allmählich verschwand. Die anderen Werte waren wie beim Erwachsenen. Die Frühgeburten zeigten normale Natriumwerte und einen leicht erhöhten Kaliumgehalt, aber sie hatten eine klare hyperchlorämische Azidose, die in der ersten Woche unverändert blieb. Die Azidose am ersten Tage führt man auf die Nachwirkungen eines anäroben Stoffwechsels in utero oder während der Geburt zurück. Die hyperchlorämische Azidose der Frühgeburten wird auf die physiologische Unreife der Niere im Hinblick auf die Chlorid-Clearance zurückgeführt. Die Elektrolytenwerte bei Frühgeburten zeigten sehr große Schwankungen, was auf die Labilität der Frühgeburten in der Erhaltung des Equilibrums der Plasmaelektrolyte hinweist.

Electrolitos plasmáticos en el período néonatal.

En 32 nacidos de término y 30 prematuros se determinaron los niveles plasmáticos de Na, K, Cl y CO_2, desde el 1° al 7° días inclusive. Los nacidos de término mostraron durante las primeras 24 horas una ligera acidosis, que desapareció gradualmente al cabo de algunos días. Los niveles de Na, K y Cl fueron iguales a los valores normales del adulto. Los prematuros tenían una natremia normal, una potasemia ligeramente elevada, y una clara acidosis hiperclorémica, que permaneció estacionaria durante la primera semana. La acidosis del primer día es atribuída a efectos residuales de un metabolismo anaeróbico in utero o durante el nacimiento. Se considera que la acidosis hiperclorémica de los prematuros es el resultado de una inmadurez funcional del riñón, en particular del clearance de cloruros. Las cifras de electrolitos plasmáticos en los prematuros mostraban una gran dispersión, lo que parece indicar una cierta labilidad en los mecanismos de mantención del equilibrio de los electrolitos del plasma.

References

Brenner, W. and Grohla, Cr.: Flammenphotometrische Kaliumbestimmung im Serum normaler Kinder. Ztschr. Kinderh. *72:* 409, 1953.

McCance, R. A. and Young, W. F.: Secretion of urine by newborn infants. J. Physiol. *99:* 265, 1941.

Earle, B. P., Bakwin, H. and Hirsch, D.: The plasma potassium level in the newborn. Proc. Soc. Exper. Biol. & Med. *76:* 756, 1951.

Hoffman, W. S., Parmelee, A. H. and Grossman, A.: Mechanism of production of acidosis in premature infants by protein milk. Am. J. Dis. Child. *75:* 637, 1948.

— Electrolyte balance studies on premature infants on a diet of evaporated milk. Am. J. Dis. Child. *77:* 49, 1949.

Kotikoff, J. A.: Über den Mineralgehalt im Blute der Kinder im ersten Lebensjahr. Jahrb. Kinderh. *138:* 280, 1933.

Reardon, H. S., Graham, B., Wilson, J. L., Baumann, M. L., Tsas, M. K. and Murayama, M.: Acid-base equilibrium and oxygen hemoglobin and hematocrit levels in premature infants. Am. J. Child. *79:* 372, 1950.

Strengers, Th. and Klinkenbergh, E. A. M.: Ervaringen met de Beckman-vlamfotometer. Chem. Weekbl. *38:* 705, 1952.

Strengers, Th. and Asberg, E. G. M.: Over een snelle microchloorbepaling. Nederl. tijdschr. geneesk. *97:* 2018, 1953.

Strengers, Th. and v. d. Kolk, M. M.: Microbepaling van de alkali-reserve. Nederl. tijdschr. geneesk. *97:* 2152, 1953.

Svendsen, A.: Potassium in infants. Acta paediat. Suppl. 77, p. 147, 1949.

Received 30.12. 1953.

Clinical Chemical Laboratory
Onze Lieve Vrouwe Gasthuis
1e Oosterparkstraat 179
Amsterdam.

Acta Pædiatrica **43**: 347—361. July 1954

From the Pediatric Clinic, Karolinska Sjukhuset, and the Department of Physical Cell Research, Karolinska Institutet, Stockholm 60.

Primary Vitamin D Refractory Rickets

I. Report of Two Cases Treated with High Doses of Vitamin D

by J. WINBERG, C. G. BERGSTRAND, B. ENGFELDT and R. ZETTERSTRÖM

Introduction

Skeletal changes resembling those found in genuine rickets (defined as a disease caused by deficiency of vitamin D) are found during various pathological conditions. Such changes occur when cartilage growth and development of bone matrix are combined with an insufficient mineralization. This may be caused either by changes in mineral metabolism or by development of a matrix incapable of undergoing mineralization. The changes are most marked in rapidly growing bones. Such changes are found when resorption of bone-salt forming ions, or of vitamin D from the gut is deficient, as in steatorrhoe (ALBRIGHT *et al.*, 1), in kidney disease with glomerular and tubular renal insufficiency (1; BOYD and STEARNS, 7), in the Debré-De Toni-Fanconi syndrome (FANCONI, 15; MCCUNE *et al.*, 24), and in liver disease (GERSTENBERGER, 18), where according to THOENES and GRUSON (28) it is due to deficient resorption of vitamin D. An insufficient skeletal mineralization is also characteristic of the rare disease which has been termed "rickets resistant to vitamin D" or "phosphate diabetes" (FANCONI, 16), and which has no etiologic connection with the aforementioned conditions.

In this disease enormous amounts of vitamin D induce a better calcification, but in contrast to genuine rickets, no real healing is achieved by vitamin D treatment. Vitamin D refractory rickets generally appears in children of between 1–2 years. Marked skeletal deformities develop rapidly, often accompanied by multiple fractures. There is an extremely low serum inorganic phosphate concentration. The disease seems to heal spontaneously in adolescence or in adult life.

Twenty to thirty fairly reliable cases have been published (2, 3, 4, 6, 8, 10, 11, 13, 14, 16, 17, 20–23, 26, 27, 29, 31), but at least twice as many cases have been reported as "rickets resistant to vitamin D", though data

given are not sufficient to exclude other primary disorders, having the sam skeletal changes as in rickets. In this paper two more cases of rickets refractor to vitamin D are reported and discussed from the clinical point of view. I a subsequent paper (32) the results of the metabolic studies during treatmen will be reported.

Case Reports

Case 1.—6 years old boy with albinism, 4th child of healthy parents. Sibling healthy. No skeletal disease among relatives. Nutrition and rickets prophylaxes ad quate. Normal development during infancy. Normal dentition. At the age of 20 month shortly after an upper respiratory infection, rapidly progressing skeletal deformitie resembling those of rickets appeared. During the next two years the boy was treate with about 20 millions I.U. of vitamin D without any effect. Table 1 shows the value of calcium and phosphate.

Findings on admission. On his first admission to the clinic, the boy was 6 years old mentally normal, but underdeveloped physically. His length was 98 cm, lower varia tion limit for Swedish boys of the same age 105 cm, and weight 14.2 kg. He was no able to walk without support. There was marked anterior femoral and tibial bowing marked scoliosis and enlargement of the epiphyses (Fig. 1). The musculature was slightly hypotonic, but the abdomen not markedly distended. The hair, skin and eyegrounds lacked pigmentation. There was a congenital nystagmus. No cystine deposits in corneae. Blood pressure 95/55 mm Hg. On skeletal X-ray there was marked rachitic and osteomalacic changes with fractures (Fig. 2 A). Microscopical examina tion of biopsy from costochondral junction revealed retarded maturation of the bone as is found in rickets (Fig. 3).

TABLE 1

Case 1. Values of calcium and phosphate in blood serum before admission. From 1948–1950 the boy was treated with about 20 million I.U. of vitamin D. The last two values after beginning of treatment in the clinic.

	Serum phosphate mg%	Serum calcium mg%	Alkaline phosphatase activity (Busch units)
1948 21. 1	1.9		
7. 4	3.5		
10.11	2.8		
24.11	1.9		
1949 24. 3	3.0	9.1	
1950 20. 3	2.9	9.8	
29. 6	3.4	8.9	
1.12	2.8		
1951 17. 8	2.4	9.5	
24. 8	3.2	9.0	
1952 17. 4	5.1	9.4	131
16. 6	6.5	14.1	69

Fig. 1. Case 1. Appearance on admission. See text.

Laboratory findings. Blood. Some of the values of calcium, phosphate and alkaline phosphatase are given in Table 1. NPN 38 mg per 100 ml, cholesterol 162. No signs of disturbed electrolyte or acid-base regulation were revealed by serum analyses. Serum protein 7.5 g per 100 ml with normal electrophoretic pattern. Wassermann reaction neg.

Urine. No albuminuria, reducing substances, nor ketone bodies. The total α-amino nitrogen excretion determined according to VAN SLYKE *et al.*[1] was 74.5 and 71.5 mg/day on two different occasions before vitamin D treatment. Double determinations were performed. Two dimensional paper partition chromatography according to DENT (12) showed that the proportions between different amino acids excreted were quite normal. Microscopically no cells, nor casts. pH about 6 in repeated determinations.

Renal function. Urine volume 3–400 ml/day. Concentration and dilution normal. Ammonia production determined after treatment and expressed as nitrogen, was 0.2 before, and 0.4 g/day after daily administration of 4 g ammonium chloride over

[1] VAN SLYKE, D., MACFADYEN, D. and HAMILTON, P.: Gasometric determination of amino acids in urine by ninhydrin-carbon dioxide method. J. Biol. Chem. *150*: 251, 1943.

Fig. 2. Case 1. X-ray of lower left leg. *A*. Before treatment. There is general decalcification with a coarse trabeculated structure. In some areas cystlike rarefactions occur, for example in the tibial epiphysis (marked by an arrow). Metaphyses as in severe rickets. Fracture of tibial and fibular shafts. *B*. In January 1953, after treatment with vitamin D and longitudinal osteotomy. Calcium content of skeleton almost normal. The cyst-like rarefactions have disappeared. Metaphyses sharply defined. Osteotomies and fractures completely healed.

4 days. Carbon dioxide combining power not influenced by the ammonium chloride load. Intravenous urography normal.

Liver function. Serum citric acid 2.2 mg per 100 ml, serum bilirubin 0.38. Thymol test 1 unit. Prothrombin time normal.

Resorption. Of 120 g of fat ingested over a three day period, only 2 per cent was recovered in faeces.

Therapy. Details of treatment and the effect of vitamin D are shown in Fig. 7. The significance of these findings in correlation with the metabolic changes will be discussed in a subsequent paper. During the two months, from the middle of March to the middle of May 1952, 22 millions I.U. of vitamin D were given. Roentgenologic

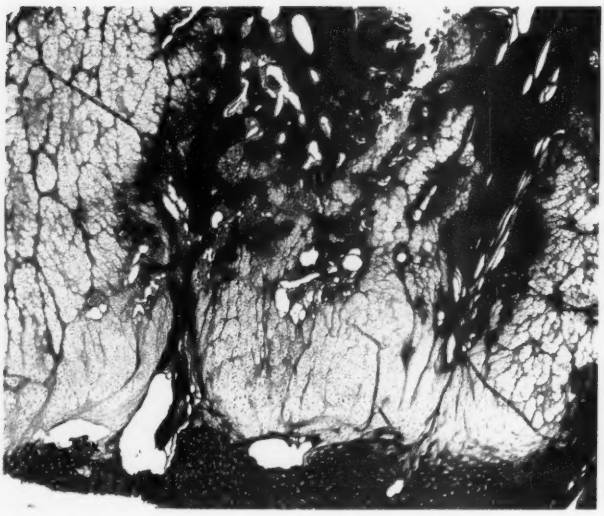


Fig. 3. Case 1. Longitudinal section through costochondral junction before treatment. Note the widening of the irregular epiphyseal plate. Magnification 50 ×.

signs of healing were demonstrable in period 18. As is seen in Table 1 the phosphatase activity decreased during this treatment. During the next three months he received 75,000 I.U. daily with further improvement. Bilateral osteotomies were performed in October 1952. After the operation, when he was immobilized for three months, he did not receive any vitamin D. In spite of this the serum phosphate concentration was still at a high level, serum alkaline phosphatase activity 38–45 units according to Busch and Busch. X-ray showed further improvement and complete healing of the osteotomies (Fig. 2 B). From February to July 1953 when he was out of bed he received no vitamin D, and the disease became more active again. At this time he could walk about fairly well and also run a little. When vitamin D therapy was started again, rapid healing occurred as revealed by clinical and roentgenological examinations.

Case 2.—Third child of healthy parents, siblings healthy, no skeletal disease among relatives. Ordinary nutrition and rickets prophylaxis. Dentition, physical and mental development were normal. At about 15 months of age, typical skeletal signs of rickets appeared. Between the ages of 18 and 24 months, the boy was treated with 3 million I.U. of vitamin D without any effect. The values of calcium and phosphate during this period are listed in Table 2.

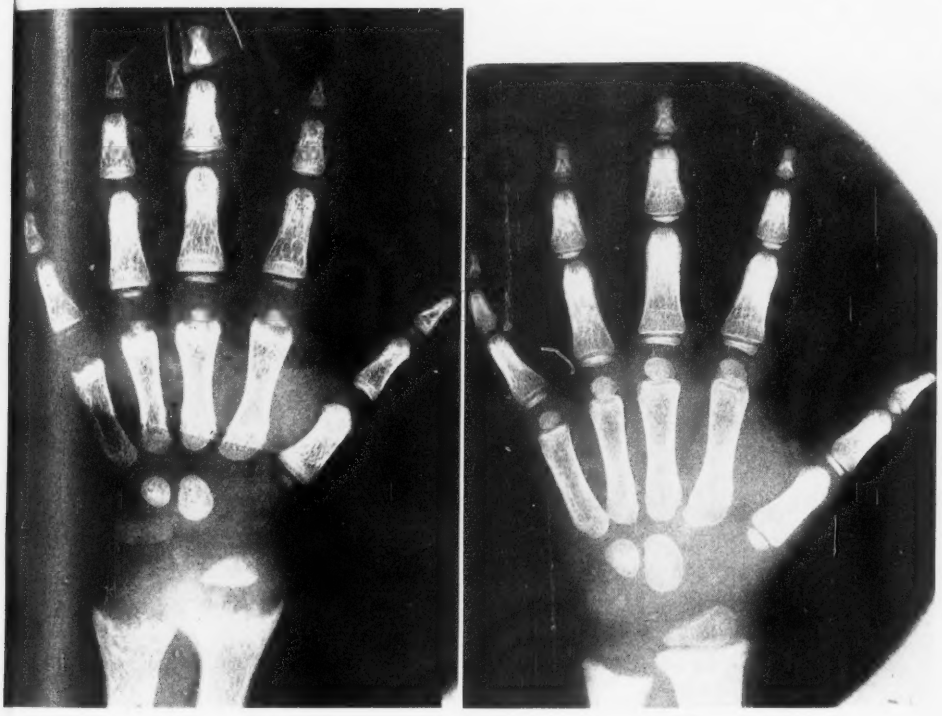
Findings on admission in October 1951. On admission to the clinic the patient was three years old, had a complete alopecia, was mentally normal, but slightly underdeveloped physically. His length was 85 cm, lower variation limit for Swedish boys of the same age 86.7 cm. The head was large, of the caput quadratum type. The epiphyses were enlarged and there was a slight anterior bowing of the legs (Fig. 4). His gait was waddling and cautious. Muscular tonus was normal, abdomen not distended. Blood pressure normal. Eyegrounds normal, no cystine deposits in the corneae. He was practically bald, with only a few solitary soft hairs. Biopsy from the capillitium

TABLE 2

Case 2. Values of calcium and phosphate in blood serum before admission. During this period the boy was treated with 3 million I.U. of vitamin D. The last values after administration of 100 million I.U. of vitamin D.

	Serum phosphate mg%	Serum calcium mg%	Alkaline phosphatase activity (Busch units)
1951 5. 1	2.8	11.8	
6. 2	2.9		
24. 2	2.1		
2. 3	2.8		
2. 4	4.0		
15.10	4.4	10.2	
1952 21. 2	4.8	9.3	134
18. 6	5.4	11.3	113

Fig. 4. Case 2. Appearance on admission. See text.



A. *B.*

Fig. 5. Case 2. X-ray. — *A*. Before treatment. Slightly reduced calcium content. Metaphyses cupped and irregular as in severe rickets. The changes less pronounced than in case 1. *B*. In September 1953 after 18 months of intensive treatment (400 million I.U. of vitamin D). Calcium content normal. Metaphyses still somewhat cupped, but outlined distinctly.

showed an almost total atrophy of the sebaceous glands and hair germinative centers. X-ray examination showed the same type of changes as in case 1 (Fig. 5A). Skeletal biopsy (rib) (Fig. 6) showed changes typical of rickets but not of the high degree seen in case 1 (by comparison with Figs. 3 and 6).

Laboratory findings. Blood. Some values of calcium, phosphate and alkaline phosphatase activity are given in Table 2. NPN 36 mg per 100 ml, cholesterol 227. Serum protein 7.0 g per 100 ml, normal electrophoretic pattern. No signs of disturbed electrolyte or acid-base regulation were revealed by serum analysis.

Urine. No albumin, reducing substance nor ketone bodies. The total α-amino nitrogen excretion determined on two occasions before vitamin D treatment was 25.0 and 42.2 mg respectively (double determinations each time). Partition chromatography normal. Microscopically no cells, nor casts. pH 5.5–6.0.

Renal function. Urine volume about 300 ml/day. Dilution and concentration normal. Intravenous urography normal. Ammonia production after treatment, given as nitrogen, was 0.45 g before, and 0.8 g/day after daily administration of 4 g ammonium chloride over 4 days. Carbon dioxide combining power fell from 27 mEq to 19 mEq.

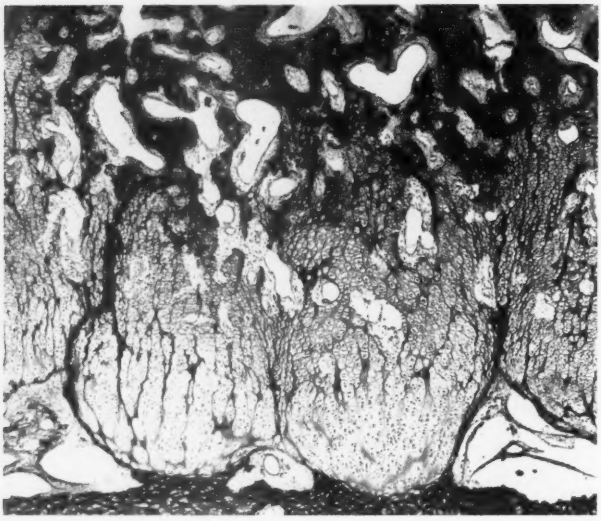


Fig. 6. Case 2. Longitudinal section through costochondral junction before treatment. The changes are typical of rickets, but not as severe as in Case 1. Magnification 50 ×.

Liver function. Serum citric acid 2.6 mg per 100 ml, serum bilirubin 0.50. Thymol test 1 unit.

Resorption. Of 90 g of fat ingested during a 3-day period, only 1.5 per cent was recovered in the faeces.

TABLE 3

Case 2. Vitamin D treatment during different periods and effect on skeleton as judged by alkaline phosphatase activity (Busch units) and X-ray. During the whole time the boy received an ample supply of calcium phosphate, and from July 1952, 6 g of sodium citrate per day.

Time	Vit. D Million I.U.	Sulkowitch's test	Alkal. phosphatase	X-ray
March 52–July 52 . .	190	neg.	130–100	May 5 52 slightly increased calcification
July 52–Nov. 52 . .	80	neg.		Nov. 11 52, epiphysis a little smoother
Nov. 52–Dec. 52 . .	90	neg.	79– 66	
Dec. 52–Sept. 53 . .	55	sometimes pos.	60–54–40	During this time roentgenological healing. Sept. 9 53 see Fig. 5 B
Oct. 53, during 3 weeks	80	sometimes pos.		

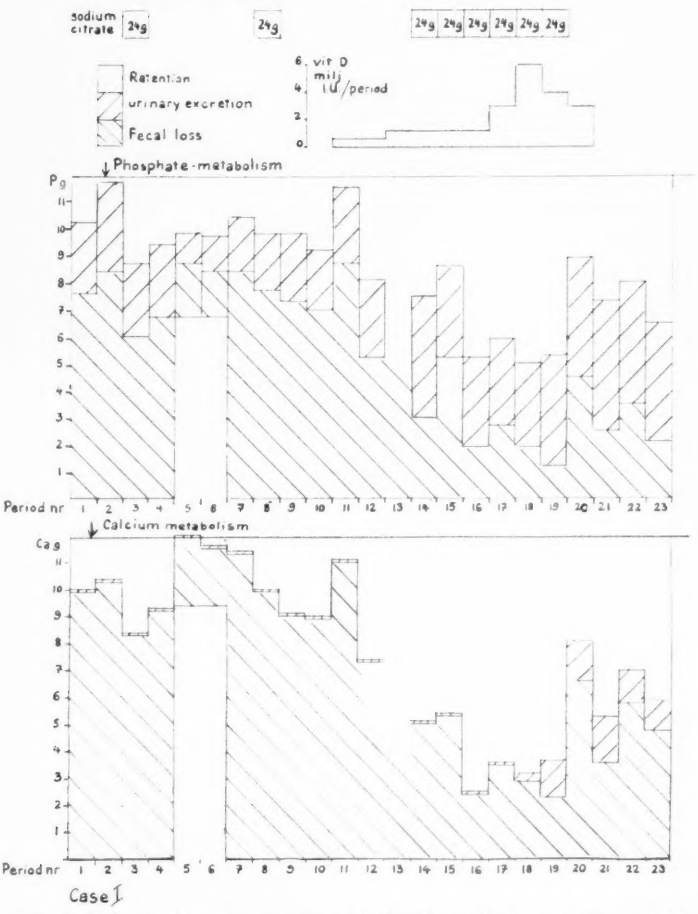

Sodium citrate
24g
24g
24g 24g 24g 24g 24g 24g
Retention
urinary excretion
Fecal loss
6. vit D mill I.U./period
4.
2.
0.
Phosphate-metabolism
Pg
Period nr 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Calcium metabolism
Ca g
Period nr 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Case 1

Fig. 7. Case 1. Balance chart for calcium and phosphate. Each metabolic period lasts for six days. Resorption of phosphate is good, the bulk of it being excreted in the urine. Reduction of phosphate excretion during periods 5 and 6 shows good ability to economize with phosphate. During restricted ingestion of calcium practically no calcium is resorbed. The resorption is improved by an ample supply of calcium and phosphate. Urinary calcium excretion is only 10–15 mg/day, also when serum calcium level is normal or increased. Vitamin D causes an increased retention of calcium and phosphate.

Therapy. The vitamin D treatment is roughly listed in Table 3. For details see Fig. 8. During this intensive treatment, the boy became successively more active, and now runs and climbs like a normal boy. Radiological examination of the skeleton in September 1953 was almost normal (Fig. 5B). The high alkaline phosphatase activity (Table 3) indicates a still active disease. The "healing" took place chiefly from December 1952 to September 1953, when he was at home. During this period no metabolic studies were performed. He did not show any symptoms of vitamin D intoxication. The Sulkowitch test which was performed every day was positive on few occasions only. Kidney function was quite normal in September 1953.

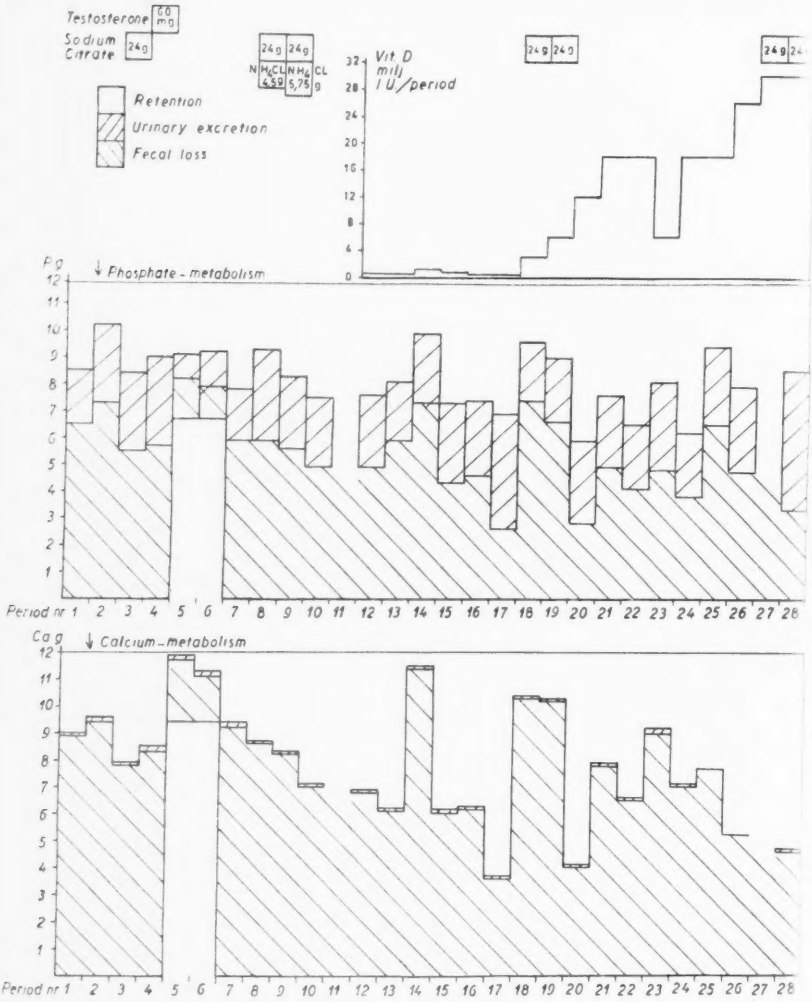

Testosterone 60 mg
Sodium Citrate 24 g
24 g 24 g
NH4CL 4,50 NH4CL 5,75 g
Retention
Urinary excretion
Fecal loss
Vit D mill I U/period
24 g 24 g
24 g 24
Fig
Phosphate - metabolism
Period nr 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
Ca g
Calcium - metabolism
Period nr 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Fig. 8. Case 2. Balance chart for calcium and phosphate. Each metabolic period lasts for s days. The pretreatment pattern is the same as in Case 1. The effect of treatment with vit min D on calcium and phosphate balance is insignificant. The treatment also fails to cau any significant effect on the bone disease as judged from the values for serum alkali phosphatase activity.

Results of Therapy

The general technique and most of the results are to be published late In this paper only the effect on calcium and phosphate balance is reporte

TABLE 4

Earlier investigations on calcium and phosphate balance in cases of rickets refractory to vitamin D. In all but one investigation, there is a positive balance, the retention being highest when the intake of calcium and phosphate is high and the Ca : P ratio most optimal.

	Obs. time in days	Intake in gram/day		Retention in gram/day	
		Ca	P	Ca	P
Case 1	24	2.0	2.0	0.4	0.32
Case 2	24	2.0	2.0	0.53	0.48
Albright et al. (2)	18	0.8	1.1	0.20	0.19
Freeman (17)	9	1.3	1.3	0.15	0.19
Highman and Hamilton (19)		0.1	0.8	−0.033	−0.51
(probable case)		1.3	1.5	+0.39	0.00

The metabolic studies, illustrated by Figs. 7 and 8, demonstrate that even in the absence of other treatment than an ample supply of calcium and phosphate, there is a positive calcium and phosphate balance, i.e. the intake is higher than the sum of urinary and fecal loss. The high retention seems remarkable and experimental errors cannot be fully excluded. An increase in the concentration of serum calcium and serum phosphate might indicate, however, that there is a definite positive balance. When the calcium intake is reduced, however, there is no longer any retention of calcium (periods 5 and 6), which is in agreement with earlier investigations. It is also the opinion of BENJAMIN and HESS (5) that the diminished retention of calcium in ordinary human rickets can be improved by increased ingestion of calcium and phosphate. As can be seen from Table 4, earlier investigations of calcium and phosphate balance in rickets, refractory to vitamin D, have also shown a positive balance, the retention being highest when the intake of calcium and phosphate is high and the ratio Ca:P most optimal.

Discussion

The two cases reported here have shown the same clinical features as cases described earlier as rickets resistant to vitamin D or as phosphate diabetes (see Introduction). The laboratory investigations have fully excluded the existence of a primary defect in resorption from the intestine, if were any signs of liver damage or renal glomerular or tubular insufficiency demonstrated. Amino acid excretion was within normal limits. In accordance with earlier reports of this disease, the two cases were, from the roentgeno-

logical point of view, cured by the administration of massive doses of vitamin D. By this treatment retention of calcium and phosphate was markedly increased as could be shown in Case 1. The alkaline phosphatase activity in the blood serum decreased.

Rachitic changes in the skeleton are known to develop secondarily to renal dysfunction, despite the absence of the ordinary signs of renal insufficiency. The X-ray picture of the skeleton in rickets refractory to vitamin D, is similar to that of the Milkman syndrome (1, 25), a disease due to deficient renal tubular function, with resulting heavy loss of fix bases, inter alia calcium, in the urine. This is in marked contrast to the extremely low calcium excretion in cases of rickets refractory to vitamin D.

FANCONI and GIRARDET (16) found an abnormally high urinary excretion of phosphate in cases of rickets refractory to vitamin D. These authors advanced the hypothesis that in this disease there is another type of primary tubular insufficiency, different from that in the Milkman syndrome, characterized by an inability to reabsorb phosphate in the kidney tubules. For that reason the disease was termed "phosphate diabetes". Since, however, the excretion of phosphate seems to be regulated by the intake, as is clearly demonstrated in periods five and six for both our cases, such a defect cannot be the primary cause of the disease. Since resorption of phosphate from the gut is relatively high, the high urinary excretion seems merely to be the result of an inability to utilize the phosphate resorbed for formation of bone salts.

Estimation of vitamin D concentration in serum have been performed according to the method of WARKANY (30) in several cases of rickets refractory to vitamin D, BAKWIN *et al.* (4), ELIOT and PARK (13), MCCUNE (23). From these investigations it can be concluded that resorption of vitamin D is not defective in this disease.

There are indications that a genetic factor is involved in the etiology of this peculiar type of rickets. The disease is often familial or hereditary (10, 11, 16, 20, 23, 26), and appears more often in males—17 out of the 26 cases published earlier. In the four hereditary cases in males (CARLGREN, CHRISTIANSEN, FANCONI, IMERSLUND), however, the disease was transmitted by the mother.

In some cases the disease has been combined with such congenital malformations as craniostenosis (20). One of our cases had defective development of pigment, and the other one of hair germinative centers as revealed by biopsy.

That the disease is not of the same type as ordinary rickets is further suggested by the fact that in spite of the seriousness of the disease only a slight muscular hypotonia could be demonstrated. If a metabolic disorder of the same type as occurs in genuine rickets is the cause of this disease,

severe hypotonia should be expected.[1] Further, there is a poor correlation between the dose of vitamin D required for "healing" and the severity of the disease, which is clearly demonstrated by the treatment of our cases. Case 2 showed much milder symptoms than Case 1, but required considerably greater doses of vitamin D for "healing". If vitamin D was a specific therapeutic agent in this disease, one would not have expected such a poor correlation between reaction to treatment and severity of disease.

As will be shown in a subsequent paper (32) healing is first demonstrable in Case 1 when a state of hyperphosphatemia is induced. The inability of the osteoid tissue to calcify to a normal degree when serum phosphate is within normal limits might indicate that the cause of the disease is a primary skeletal disorder, or that there is a disturbance of some yet unknown metabolic process regulating calcification.

The term "rickets resistant to vitamin D" may for good reasons be applied to several types of rickets of various etiology. The disease which has been discussed in this paper seems to be a well defined clinical entity and we suggest the name "Primary Vitamin D Refractory Rickets". This name would imply that the disease is not secondary to any known disorder of nutrition, resorption or kidney function.

Summary

1. Two cases of rickets resistant to vitamin D are described.

2. The effect of massive doses of vitamin D on calcium and phosphate balance is studied.

3. This disease is a well defined clinical entity and the name "Primary Vitamin D Refractory Rickets" is suggested. The nature of the disease is unknown, but it seems likely that the pathogenetic mechanism is different from that in genuine rickets.

Rachitisme primaire résistant à la vitamine D. I. Observations de 2 cas traités par de hautes doses de vitamine D.

Les auteurs décrivent deux cas de rachitisme résistant à la vitamine D, et étudient les effets de hautes doses sur la balance du calcium et des phosphates. Cette affection correspond à une entité clinique bien définie, et les auteurs proposent le nom de «Rachitisme primaire réfractaire à la vitamine D». La nature de la maladie semble différente de celle de l'authentique rachitisme.

Primäre D-Vitamin-resistente Rachitis. I. Bericht über 2 mit hohen Vitamin-D Dosen behandelte Fälle.

Es werden 2 Vitamin-D-resistente Rachitisfälle beschrieben. Der Einfluß massiver Vitamin-D Dosen auf den Kalzium- und Phosphathaushalt wurde studiert. Diese

[1] JONXIS and HUISMAN (Lancet II: 428, 1953) pointed out that in human rickets there is an increased urinary α-amino nitrogen excretion with a pathological partition pattern of the different amino acids. In vitamin D refractory rickets there are no such changes as is revealed in our cases. These findings merely stress the different pathogenesis of ordinary rickets and vitamin D refractory rickets, the former being a generalized metabolic disorder.

Krankheit stellt eine scharf umschriebene klinische Einheit dar, für die der Name „Primäre D-Vitamin refraktäre Rachitis" vorgeschlagen wird. Die Natur der Krankheit ist unbekannt, aber es ist wahrscheinlich, daß der pathogenetische Mechanismus von dem der genuinen Rachitis verschieden ist.

Raquitismo primario refractario a la vitamina D. I. Comunicación acerca de dos casos tratados con altas dosis de vitamina D.

Se describen dos casos de raquitismo vitamino-D-resistentes. Se estudia el efecto de dosis masivas de vitamina D sobre el balance calcio-fósforo. Esta enfermedad es una entidad clínica bien definida, para la cual se sugiere el nombre de «Raquitismo primario refractario a la vitamina D». Aunque su naturaleza íntima es desconocida, su patogenia probablemente es diferente a la del raquitismo genuino.

References

1. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C. Jr and Roos, A.: Osteomalacia and late rickets: The various etiologies met in the United States with emphasis on that resulting from a specific form of renal acidosis, the therapeutic indications for each etiological subgroup, and the relationship between osteomalacia and Milkman's syndrome. Medicine *25:* 399, 1946.
2. Albright, F., Butler, A. M. and Bloomberg, E.: Rickets resistant to vitamin D therapy. Am. J. Dis. Child. *54:* 529, 1937.
3. Albright, F. and Reifenstein, E. C.: The parathyroid glands and metabolic bone disease. Williams and Wilkins Co. Baltimore 1948.
4. Bakwin, H., Bodansky, O. and Schorr, E.: Refractory rickets. Am. J. Dis. Child. *59:* 560, 1940.
5. Benjamin, H. R. and Hess, A. F.: The forms of the calcium and inorganic phosphorus in human and animal sera. I. Normal, rachitic, hypercalcemic and other conditions. J. Biol. Chem. *100:* 27, 1933.
6. Bessau, G. and Löhr, H.: Über eine Heilungsmöglichkeit gewisser Vitamin D resistenter Rachitisformen. Monatsschr. Kinderh. *90:* 1, 1942.
7. Boyd, J. D. and Stearns, G.: Late rickets resembling Fanconi syndrome. Am. J. Dis. Child. *61:* 1012, 1941.
   Concomitance of chronic acidosis with late rickets. Am. J. Dis. Child. *64:* 594, 1942.
8. Butler, A. M.: Discussion on Dr Kajdi's report (21).
9. Camerer, J. W.: Vitamin-D-resistente Rachitis. Monatsschr. Kinderh. *96:* 68, 1948–49.
10. Carlgren, L.-E.: A case of vitamin D resistant rickets treated with massive doses of vitamin D. Acta pædiat. *35:* 367, 1948.
11. Christensen, J. F.: Three familial cases of atypical late rickets. Acta pædiat. *28:* 212, 1952.
12. Dent, C. E.: The aminoaciduria in Fanconi syndrome: A study making extensive use of techniques based on paper partition chromatography. Biochem. J. *41:* 240, 1947.
13. Eliot, M. M. and Park, E. A.: Rickets, in Brennemann's Practice of Pediatrics. Vol. I. Chapter 36. W. F. Prior and Co. Hagerstown, Maryland. 1939.
14. Engleson, G.: Refractory rickets. Acta pædiat. *38:* 135, 1949.
15. Fanconi, G.: Der frühinfantile nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis. Jahrb. Kinderh. *147:* 299, 1936.
16. Fanconi, G. and Girardet, P.: Familjärer persistierender Phosphatdiabetes mit D-vitaminresistenter Rachitis. Helvet. paediat. acta *7:* 14, 1952.
17. Freeman, S. and Dunsky, I.: Resistant rickets. Am. J. Dis. Child. *79:* 409, 1950.
18. Gerstenberger, H. J.: Rachitis hepatica. Monatsschr. Kinderh. *56:* 217, 1933.
19. Highman, W. J. and Hamilton, B.: Calcium and phosphorus metabolism in a case of intractable rickets. J. Pediat. *9:* 56, 1936.
20. Imerslund, O.: Craniostenosis and vitamin D resistant rickets. Acta pædiat. *40:* 449, 1951.
21. Kajdi, L.: Comparison of the effect of vitamin D and citrates on mineral metabolism in late rickets. Am. J. Dis. Child. *68:* 352, 1944.
22. Lüssy, M.: Über sogenannte Vitamin-D-resistente Rachitis. Ann. paediat. *166:* 11, 1946.
23. McCune, D. J.: Refractory rickets in identical twins. Am. J. Dis. Child. *63:* 1008, 1942.

24. McCune, D. J., Mason, H. H. and Clark, H. T.: Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome): Report of case in which increased urinary organic acids were detected and identified, with review of the literature. Am. J. Dis. Child. *65:* 81, 1943.
25. Milkman, L. A.: Multiple spontaneous idiopathic symmetrical fractures. Am. J. Roentgenol. *32:* 622, 1934.
26. Robertson, B. R., Harris, R. C. and McCune, D. J.: Refractory rickets: Mechanism and therapeutic action of Calciferol. Am. J. Dis. Child. *64:* 948, 1942.
27. Talbot, N. B., Sobel, E. H., McArthur, J. W. and Crawford, J. D.: Functional Endocrinology. Harward University Press, Cambridge, Mass. 1952. P. 72.
28. Thoenes, F. and Gruson, W.: Zur Frage der "Rachitis hepatica". Monatsschr. Kinderh. *67:* 134, 1936.
29. Wallgren, A.: Resistente Rachitis. Arch. Kinderh. *141:* 179, 1951.
30. Warkany, J.: Estimation of vitamin D in blood serum. Am. J. Dis. Child. *52:* 831, 1936.
31. Woolley, P. V.: Rickets resistant to the usual doses of vitamin D. J. Pediat. *33:* 118, 1948.
32. Zetterström, R. and Winberg, J.: Primary vitamin D refractory rickets. II. Metabolic studies. To be published.

Received 8.1. 1954.

Barnkliniken
Karolinska sjukhuset
Stockholm 60.

Acta Pædiatrica **43**: 362—367. July 1954

Breast or Cow's Milk as Infant Food

Discussion on the Methods of Comparison

by GERT v. SYDOW, M.D., Sundsvall,
and NILS FAXÉN, M.D., Gothenburg

The question as to whether, and to what extent, breast milk is superior to other milk for infant feeding, is of fundamental importance in pediatrics and has been discussed frequently throughout the whole history of pediatrics. The reason why no general agreement has yet been reached is not hard to find out: it is difficult both to select irreproachable series for comparison, and to make faultless comparisons of these. Some examples will show this.

In order to compare the mortality of breast-fed and bottle-fed infants in a community, it is first necessary to investigate whether there are any other than feeding differences between the groups, for these are usually present. The infant of a careless and indolent mother will probably be bottle-fed, and, at the same time, it will also run the risk of not being properly cared for. By contrast, an ambitious and painstaking mother will most probably breast-feed her child, especially in our community where, in most places, intense breast-feeding propaganda is carried on. As a result of this propaganda, there are also, in our community, more breast-fed infants among the more enlightened social classes, than in those less enlightened. If one finds, then, in a population, a higher mortality in bottle-fed infants than in the breast-fed, one cannot conclude from this that the difference depends on the type of feeding. There may also be other causes.

If, on the other hand, comparisons are made between two groups of infants cared for in a Children's Home, the risk of comparing groups with different social structure and different quality of care may be avoided. In such a case it is hardly possible to compare the mortality, because the series will be too small for such a comparison. Other criteria of the results of feeding must be sought for, e.g., the growth rate or the resistance against infection. In comparing, however, one group of breast-fed infants cared for in a Children's Home together with their mothers, with a group of bottle-fed children cared for without their mothers in another part of the Home, all sources of error are still not avoided.

In comparing the rate of growth, one must make clear that in the one group, the infant has been allowed, on the whole, to take as much as it wants, while in the other group, the infant has been given meals of prefixed quantity and nutritional value. It is to be expected, then, that the comparison will turn out differently, depending on whether these meals consist of high-caloric mixtures in a rather large quantity, or of more diluted mixtures in comparatively small amounts. If one finds, therefore, that the breast-fed infants grow faster than the bottle-fed ones, this *may* simply mean that the bottle feeds should have been increased slightly.

In comparing the occurrence of infection in breast- and bottle-fed infants, it must be ascertained whether the risk of infection was really equally great in both groups. In most cases, this probably has not been so. In a modern Infants' Home, the prevention of infection will, as a rule, be so well carried out, that some infants may not have been exposed to any infection at all during their stay in the Home. It may depend on mere chance if an infection becomes rather widely spread in one ward but is not carried to another. In the ward for nursing mothers, each child will be cared for mainly by its mother, while in the ward for orphans, every nurse has the care of more than one child. If one of the staff contracts an infection, this may, therefore, be expected to spread more widely than if it is introduced by a mother. It may also happen that the staff have more contact with the community outside the Home than have the mothers during their stay, and that, therefore, in spite of all control, the risk of introducing an infection is greater, even from this cause, in the ward where the children are cared for exclusively by the staff. Of course, it is also conceivable that the risk may be greater in the mothers' department, because of the more frequent visits from relatives and friends.

In addition, in a comparison between breast- and bottle-fed infants, not only is the food different, but also the method of feeding. The role played by the breast feeding itself, through the sense of security and satisfaction it may give to the infant, as regards growth resistance against infection, and perhaps mortality rate, cannot be gauged, except by comparing a series of breast-fed infants with a series of infants fed under otherwise identical conditions with collected breast milk. Such a series of sufficient size would probably be very difficult to collect.

If, on the other hand, one wants to investigate whether breast milk is superior to cow's milk formulas as a food, it is obviously necessary to give both foods in the same way, i.e. by bottle, while at the same time making sure that other care factors, staff, prevention of infection, are the same. We are going to relate here an attempt at such a comparison.

This investigation was carried out at the Infants' Home "Gullbergsbrohemmet" Gothenburg during the years 1945 until and including 1950. At this point we wish

to express our sincere gratitude to the Matron and Staff of the Home, for their willi co-operation and the great amount of extra work done in carrying through this i vestigation. During this period, every other child admitted to the orphan departme of the Home before the age of three months (from the Obstetric Hospitals, the paren homes, or the department of the Home for nursing mothers) was given collected brea milk from the Breast Milk Bank. The other alternate children were given the usu cow's milk formulas. The series had to be interrupted on some occasions owing shortage of collected breast milk, and therefore includes only 24 infants in each grou in the cow's milk group, 14 infants have been given citric acid whole milk, and 1 half or two-thirds milk mixtures. Both the groups are comparable as regards bir weight and age on admission. In the breast-milk group the birth weight varied betwe 2,250 and 4,020 g (Median 3,425 g, half the number of birth weights was between t quartiles 3,100 and 3,740 g); in the cow's milk group the variation was between 2,06 and 4,740 g (median 3,310, quartiles 3,030 and 3,995 g). The age on admission varie in the breast-milk series between 6 and 72 days (median 25½, quartiles 13½ and 4 days), in the cow's milk group between 6 and 81 days (median 41, quartiles 20½ and 54½ days). In both groups nearly all the infants had been partly or entirely breast-fed or given collected breast-milk before the beginning of the comparison.

The increase in weight has been calculated for the age periods 61–90 and 91–12 days. In the breast-milk group it varied for the first-named period between 400 and 1,050 g (median 750, quartiles 650 and 860 g) and for the latter period between 40 and 1,300 g (median 770, quartiles 655 and 875 g). For the 14 citric-acid milk infant it varied, during the first period between 330 and 1,100 g (median 780, quartiles 63 and 900) and during the latter period between 380 and 1,140 g (median 705, quartile 600 and 850 g). For the 10 infants fed with diluted formulas it varied in the earlie period between 420 and 870 g, and in the later one between 90 and 750 g. The group are obviously too small to permit, from this, of any definite conclusions.

In this study the main interest has been directed towards the frequency of infection. For investigating this, the Gullbergsbrohemmet is well suited. Housed in an old building (built in the 1720's to serve as a prison for female criminals) it consists of very large rooms with few isolation facilities. The children are admitted to units of 3–4 beds, where they are allowed to stay till between 3 and 4 months of age, when they are moved into wards of 1 beds. Breast-milk and cow's milk fed infants were placed in the same ward and were cared for by the same nurse, so the chance of contracting an in fection must be regarded as equal in both groups.

The number of days with a rise in temperature has been chosen as an inde for the occurrence of infection. It has not been possible to choose the numb of fever periods, because there is sometimes doubt as to whether a seri of days with temperature should be considered as one or two fever period It is obvious, however, that the difference between the two groups whic can be obtained from the comparison of the number of fever days correspond to a similar difference in the number of temperature periods. The differenc accordingly, is not due to a different duration of the fever periods but to different number of illnesses in the groups. Most of the fever periods hav

TABLE 1

Age groups, months (three-month periods)	0–2	1–3	2–4	3–5	4–6	5–7	6–8	7–9
Breast milk								
Total days of observation . .	1 377	1 709	1 578	1 248	923	665	430	235
Days with fever 38.1° and above	3	5	6	8	7	6	2	4
Days with subfebr. temp. 37.6°–38.0°	26	45	59	86	85	66	23	4
Total days with rise in temp. 37.6 and above	*29*	*50*	*65*	*94*	*92*	*72*	*25*	*8*
Artificial food								
Total days of observation . .	1 151	1 664	1 853	1 771	1 547	1 219	952	630
Days with fever 38.1° and above	1	10	12	20	29	34	37	24
Days with subfebr. temp. 37.6°–38.0°	52	99	146	158	165	129	94	45
Total days with rise in temp. 37.6 and above	*53*	*109*	*158*	*178*	*194*	*163*	*131*	*69*

been thought due to sore throats and similar upper respiratory infections. In some cases it has been a question of diarrhoea, varicella etc., while in others the cause of fever has not been recorded.

The number of days with a rise in temperature is shown in Table 1. In all the three-month periods there have been many more days with a rise in temperature in the cow's milk group than in the breast-milk group. This is true when comparing the number of days with fever 38.1°C and above, as well as days with subfebrile temperature 37.6°–38.0°, or the total number of days with a rise to at least 37.6°C (Tab. 2). In the latter case, the difference is statistically verified up to the fifth month of life, inclusive. It is verified for the third trimester of life too, but this may be due to defects in the material: the breast milk series at this age has greatly diminished (because the supply of breast milk did not always permit long experiments) and is possibly no longer representative.

On the whole it would be premature, from this small series, to draw any definite conclusions. The investigation may indicate that infants fed with collected (sterilized) breast milk will show, during the first months of life, a higher resistance against infection, than infants fed with cow's milk formulas, but this result must be verified by investigations on a considerably larger scale, before it can be considered definitely proved. The purpose of this paper, the writing of which was stimulated partly by the recent investigation by ALLENSWÄRD, is only to discuss the methods for comparing breast milk

TABLE 2

Number of days with rise in temperature to at least 37.6°, in per cent of tot number of days of observation

Age groups, months (three-month periods)	0–2	1–3	2–4	3–5	4–6	5–7	6–8	7–9
Breast milk	2.1	2.9	4.1	7.5	9.9	10.8	5.8	3.4
	±0.39	±0.41	±0.50	±0.75	±1.03	±1.20	±1.13	±1.18
Artificial food	4.6	6.6	8.5	10.0	12.5	13.4	13.8	11.0
	±0.62	±0.61	±0.65	±0.71	±0.84	±0.98	±1.12	±1.25
Difference	*2.5*	*3.7*	*4.4*	*2.5*	*2.6*	*2.6*	*8.0*	*7.6*
	±0.73	*±0.74*	*±0.82*	*±1.03*	*±1.33*	*±1.55*	*±1.59*	*±1.72*

and cow's milk feeding and to exemplify how such a comparison could be planned.

It should be re-emphasized that the present comparison does not tell anything about the difference between breast and bottle feeding, but only between feeding sterilized breast milk and cow's milk mixtures. It cannot be excluded that the difference would have increased had the cow's milk mixtures been compared to fresh breast milk, nor that feeding at the breast would be better than feeding collected breast milk. The last-mentioned comparison—if it is at all possible to carry out—must be planned in quite a different way.

Summary

In order to find out whether breast milk feeding is superior to artificial foods for infants, one should first make sure that the groups for comparison are identical in all respects other than feeding: e.g., that one group does not get more careful nursing or better social surroundings than the other, that the supply of food is equally free or rationed in both groups, and that the risks of infection are the same. Such a comparison may best be carried out in a Children's Home where every other child is given collected breast milk, and the others artificial food, and where all the children are nursed together under equal risks of infection. As an example, a very limited investigation of this kind is described, where the number of days with a rise in temperature was found to be considerably higher in the cow's milk group than in the breast-milk group.

Lait de femme ou lait de vache dans l'alimentation du nourrisson.

Avant d'établir toute comparaison sur les deux modes d'alimentation, il faut d'abord s'assurer que les éléments de vie, autres que la nourriture sont identiques. Les deux groupes à comparer doivent présenter les mêmes caractéristiques: Identité des soins et de milieu social, identité de limitation ou de liberté dans la ration alimentaire, identité des risques d'infection. Une telle comparaison ne peut être réalisée que dans une pouponnière; l'un des groupes recevant du lait maternel collecté, l'autre une al-

alimentation artificielle; tous les enfants étant soignés ensemble et supportant des risques infectieux semblables. Peu de recherches de ce type ont été décrites. Dans notre cas, le nombre des jours avec une élévation thermique dans les deux groupes était trouvé bien plus élevé chez les enfants recevant du lait de vache.

Brustmilch oder Kuhmilch als Säuglingsnahrung.

Um festzustellen, ob Brustmilchernährung bei Säuglingen der künstlichen Ernährung überlegen ist, muß man sicher sein, daß die Vergleichsgruppen in jeder Beziehung, nicht nur im Hinblick auf die Ernährung, übereinstimmen; d. h. daß nicht die eine Gruppe sorgfältigere Pflege erhält oder eine bessere soziale Umgebung hat als die andere, daß die Nahrungszufuhr entweder frei oder rationiert in beiden Gruppen ist, und daß das Infektionsrisiko gleich groß in beiden Gruppen ist. Solch ein Vergleich kann am besten in Kinderheimen ausgeführt werden, in denen die eine Gruppe eingesammelte Brustmilch erhält und die andere künstlich ernährt wird, und wo alle Kinder zusammen gepflegt werden, und alle dem gleichen Infektionsrisiko ausgesetzt sind. Als Beispiel wird eine sehr begrenzte Untersuchung dieser Art beschrieben, bei der die Zahl der Tage, an denen Temperatursteigerungen gefunden wurden, in der Kuhmilchgruppe bedeutend höher war als in der Brustmilchgruppe.

Leche materna o leche de vaca, como alimentos del lactante.

A fin de determinar si la crianza con leche materna es superior a la alimentación artificial del lactante, es indispensable, en primer lugar, asegurarse de que los grupos por comparar sean semejantes en todo, excepto en la alimentación diferente. Es decir, debe cuidarse que ninguno de los grupos tenga mejor atención o viva en un medio social más favorable que el otro; que la alimentación sea igualmente ad libitum o racionada en ambos grupos, y que los riesgos de infección sean los mismos. Una comparación de este tipo puede hacerse en mejores condiciones en un Hogar Infantil, en que todos los niños reciben iguales cuidados y están sometidos a idénticos riesgos de infección, dividiéndose a los niños en dos grupos: uno que recibe solamente leche, de un stock de leche de mujer, y el otro alimentación artificial. Se describe, como un ejemplo, una muy limitada investigación de este tipo, en que se demuestra que el número de días en que pudo detectarse alzas térmicas fué considerablemente superior en el grupo de niños alimentados con leche de vaca que en el grupo que recibía leche de mujer.

Reference

GYLLENSWARD, C.: Acta Soc. med. upsalien. *58*: 285, 1953.

Received 10.1. 1954.

Children's Department
Länslasarettet
Sundsvall, Sweden.

Acta Pædiatrica **43**: 368–373 July, 1954

From the Pediatric Clinic, Karolinska Sjukhuset, Stockholm.

Infants of Diabetic Mothers

I. Foetal Hypoxia in Maternal Diabetes

Preliminary Report

by G. BERGLUND and R. ZETTERSTRÖM

The diabetic state in the mother is associated with a much higher mortality rate in the foetus and newborn than that which occurs in uncomplicated pregnancies (for references cf. WHITE and HUNT, and MILLER). The risk of foetal death rises steadily throughout the pregnancy and is especially high during the last weeks before term (KOLLER). The reason for the high mortality rate is still unknown. It has, however, been suggested that some endocrinological dysfunction due to the maternal diabetes may be the cause (WHITE, TITUS, JOSLIN and HUNT).

As with some infants extracted by caesarean section and in many prematurely born infants hyaline membranes are often the direct cause of death. The clinical and pathological findings are in many respects the same as those found in morbus haemolyticus neonatorum (MILLER, JOHNSON and DUBLACHER), a disease which in severe cases is accompanied by an intrauterine anaemic hypoxia. In both conditions there is very often a general hydrops. The extramedullary erythropoiesis in the liver is abnormal (MILLER and WILSON), and the islets of Langerhans are hyperplastic (DUBREUIL and ANDERODIAS, POTTER, SECKEL and STRYKER). Quite recently WALKER and TURNBULL have reported data suggesting that the high infant mortality rate in postmaturity is due to the intrauterine hypoxia which appears a few weeks following the expected date of delivery.

In this communication some preliminary results are reported which suggest that intrauterine hypoxia might be one of the factors responsible for the low vitality of the foetus and newborn of diabetic mothers.

Methods

Capillary blood was used in the haematological investigations. The blood samples were taken under conditions as uniform as possible. Usually, the first sample was taken 3–4 hours after birth. For the determination of the haemoglobin level a photometric colorimeter was used. The photometer had been standardized against the oxy-

gen capacity, the factor 1.36 was applied. The number of nucleated red cells was estimated according to directions given by MOLLISON, and allowance was made for uneven distribution of nucleated red blood cells in the blood smears.

The oxygen content in the cord blood was determined in some cases where delivery was by caesarean section before the onset of labour. Local anaesthesia was used in all deliveries, ether being given during the extraction of the foetus. All mothers were in a satisfactory condition during the operation. Immediately on extraction of the child two clamps were placed on the umbilical cord at a mutual distance of 15 cm. From the isolated segment samples were obtained anaerobically by puncture of the vessels. The oxygen content and the oxygen capacity was determined according to VAN SLYKE and NEILL or according to BRINKMAN. In each case duplicate determinations from the venous blood in the umbilical cord were performed.

Material

Haematological examinations were performed in 19 consecutive infants born to diabetic mothers admitted to this hospital. The birth weights of the infants varied between 1,700 and 5,000 g. The foetal ages ranged between 28 and 40 weeks. The infants showed in varying degrees the clinical symptoms typical of infants of diabetic mothers. However, the series cannot be regarded as fully representative of newborns of diabetic mothers, since the uncomplicated cases were not admitted to the paediatric clinic. Of the cases studied, four died in the first two days, all of them showing symptoms of respiratory and circulatory failure. At autopsy changes typical of hyaline membranes were observed.

The oxygen saturation in the umbilical cord was determined in four infants of diabetic mothers and in two control cases.

Results

As is seen from Table 1 the number of nucleated red blood cells was abnormally high in the first day of life in 9 out of 19 children. According to ANDERSON the number of nucleated red blood cells averages 7.3 per 100 white cells in full-term infants, and 21 per 100 in prematurely born infants. In our investigation the number of nucleated red cells in normal full-term infants ranged between 0 and 1,200 per mm^3, the values thus being in good agreement with those found by ANDERSON. In all cases with an abnormally high number of nucleated red cells the direct Coombs' test was carried out to exclude possible cases of morbus haemolyticus neonatorum. The test was negative in every case. As is shown in Table 2 the nucleated red cells rapidly disappear from the blood. The results are in agreement with those obtained by MILLER and WILSON.

The abnormally high number of nucleated red cells is not an indication of increased erythropoiesis due to haemolytic anaemia. The mean haemoglobin concentration in capillary blood 3 hours after birth was 19.0 g per 100 ml (standard deviation of 2.3, estimated from the range). In normal full-term infants OETTINGER and MILLS found a mean haemoglobin value of 20.3 g

TABLE 1

Number of nucleated red cells in the first day of life in infants of diabetic mothers.

Case No.	Number of nucleated red cells	Case No.	Number of nucleated red cells
1	76,000	10	8,800
2	20,000	11	970
3	3,400	12	1,600
4	60	13	710
5	3,600	14	0
6	5,000	15	1,800
7	11,600	16	0
8	9,200	17	0
9	3,300	18	800
		19	1,700

TABLE 2

Number of nucleated red cells in the first week in two infants of diabetic mothers.

Case 2		Case 7	
Day of life	Number	Day of life	Number
1st	20,000	1st	11,600
2nd	15,600	2nd	13,300
3rd	8,000	3rd	4,700
6th	440	6th	50

per 100 ml under the same general experimental conditions. In the present material the haemoglobin level ought to be considerably lower than in normal material because of caesarean section delivery in which the umbilical cord was clamped early. Another reason for this conclusion is that the infants on an average were 4–5 weeks prematurely born. Newborn infants of diabetic mothers are more hydropic than are normal newborns. It thus seems likely that they, like children with haemolytic disease of the newborn (MOLLISON), have an increased blood volume. Thus, it can be suspected that infants of diabetic mothers have a still higher total quantity of haemoglobin than that indicated by their haemoglobin levels.

Therefore, the increased production of red cells merely seems to be produced by a fall of the oxygen supply to the foetus. ANDERSON found that

TABLE 3

Oxygen saturation in the umbilical vessels in four infants of diabetic mothers and two control cases.

Case	Gestation time	Oxygen saturation in umbilical cord	
Diabetes of the mother	Weeks	Vein per cent	Artery per cent
1	34	20	15
2	34	52	36
3	35	22	14
4	36	70*	
Clinically normal pregnancies			
1	40	79	
2	40	88	

*) The value is too high due to contamination with air.

the number of erythroblasts in the cord blood was abnormally high in children who died immediately after birth, and in children with asphyxial symptoms that might be the consequence of intrauterine hypoxia. On the other hand, there was no evidence of an increase in the number of nucleated red cells following short periods of perinatal asphyxia. Table 3 shows that intrauterine hypoxia very probably is present in many cases of maternal diabetes. In three cases the oxygen saturation in the umbilical vein is considerably lower than that from the two clinically normal pregnancies that were examined. In two cases of maternal diabetes the values are as low as those found by WALKER and TURNBULL in severe pre-eclampsia. Case number 1 died 26 hours after birth, case number 4 died 15 hours after birth. The other two cases presented perinatally the typical symptoms of maternal diabetes but improved in a few days. WALKER and TURNBULL found in normal pregnancies terminated at term an oxygen saturation in the umbilical vein of about 60 per cent. The discrepancy in oxygen saturation between our normal cases and the normal ones investigated by WALKER and TURNBULL might be due to differences in anaesthesia.

Discussion

Intrauterine hypoxia may account for some of the symptoms found in newborn babies of diabetic mothers. Clinical and pathological findings are similar to those observed in haemolytic disease of the newborn. In the latter

condition the symptoms may partly be due to the effects of anaemic hypoxia produced by the intrauterine haemolysis. The haemorrhagic tendency which is present in both states might be the result of circulatory failure due to hypoxia since there are no signs of disturbance of the coagulation mechanism. In the newborns of diabetic mothers included in this material skin petechiae were found in five cases during the first day of life. The cause of the intrauterine hypoxia cannot at present be established. It is possible that those changes inducing foetal death following postmaturity (YOUNG and BARCROFT) may start earlier in maternal diabetes than in uncomplicated pregnancies. The gaseous exchange may also be affected because of lesions in the uterine vessels.

Since the high incidence of foetal deaths and the low vitality of the newborns seem partly to be due to hypoxia, it appears logical to interrupt the pregnancy before the foetus has been subjected to serious intrauterine anoxia. It seems most advisable therefore to interrupt the pregnancy when it exceeds 35–36 weeks. If the infants are born more prematurely the perinatal mortality will be very high. More prematurely born infants of diabetic mothers seem, like those with haemolytic disease of the newborn, to have a lower vitality than other prematurely born infants.

Summary

The clinical and pathological features in newborn infants of diabetic mothers are in many respects the same as those in haemolytic disease of the newborn. The abnormally high level of nucleated red cells in the blood must be the consequence of increased erythropoiesis. This is assumed to be caused by an attempt of the foetus to raise its oxygen-carrying capacity. The finding that the oxygen content in the umbilical vein is lower than in control pregnancies seems to give support to this hypothesis.

Les enfants nés de mère diabétique. I. Hypoxie foetale au cours du diabète maternel.

L'aspect clinique et pathologique des enfants nés de mère diabétique présente de nombreuses analogies avec celui de la maladie hémolytique du nouveau-né. L'élévation anormale du taux des hématies nucléées doit être la conséquence de l'augmentation de l'érythropoïèse. Elle semble en rapport avec une réaction du foetus destinée à accroître le pouvoir oxyphorique du sang. Les auteurs ont constaté une diminution de l'oxygène dans le sang de la veine ombilicale par rapport à un groupe de contrôle, ce qui paraît en faveur de leur hypothèse.

Kinder diabetischer Mütter. I. Foetale Hypoxie bei mütterlichem Diabetes.

Das klinische und pathologische Bild bei Neugeborenen diabetischer Mütter ähnelt in vieler Hinsicht dem beim Morbus haemolyticus des Neugeborenen. Der anormal hohe Gehalt des Blutes an kernhaltigen roten Blutkörperchen muss eine Folge der gesteigerten Erythropoese sein. Man glaubt die Ursache dazu in einem Versuch des Foetus zu sehen, das Sauerstoffbindungsvermögen zu erhöhen. Die Tatsache, dass der Sauerstoffgehalt des Nabelvenenblutes geringer ist als bei Kontroll-Graviditäten scheint diese Hypothese zu stützen.

Niños de madres diabéticas. I. Hipoxemia fetal en diabetis maternal.

Los hallazgos clínicos y patológicos en los niños recién nacidos de madres diabéticas son similares en muchos aspectos a los que se encuentran en las enfermedades hemolíticas del recién nacido. El número anormalmente alto de células nucleadas en la sangre debe ser la consecuencia de una eritropoiesis aumentada. Esta estaría determinada por el intento del feto para alcanzar su capacidad para conducir el oxígeno. El hecho que el oxígeno contenido en la vena umbilical es mas bajo que en embarazos de control parace afirmar esta hipotesis.

References

Anderson, G. W.: Studies on the nucleated red cell count in the chorionic capillaries and the cord blood of various ages of pregnancy. Am. J. Obst. & Gynec. *42:* 1, 1941.

Barcroft, J. and Young, I. M.: Internal oxygen environment of brains of post-mature rabbit embryos. J. Exper. Biol. *21:* 70, 1945.

Brinkman, R. and Zijlstra, W. G.: Fundamentals and applications of clinical oximetry. van Gorcum and Comp. Assen. 1951.

Dubreuil, G. and Anderodias, J.: Ilots de Langerhans géants chez un nouveau-né, issue de mère glycosurique. Compt. rend. Soc. biol. *2:* 1490, 1920.

Koller, O.: Diabetes and pregnancy. Acta obstet. gynec. scandinav. *32:* 80, 1953.

The Fifth M & R Pediatric Research Conference. Pulmonary hyaline membranes. Philadelphia. 1952.

Miller, H. C.: The effect of diabetic and prediabetic pregnancies on the foetus and newborn infant. J. Pediat. *29:* 455, 1946.

Miller, H. C., Johnson, R. D. and Durlacher, S. H.: A comparison of newborn infants with erythroblastosis foetalis with those born to diabetic mothers. J. Pediat. *24:* 603, 1944.

Miller, H. C. and Wilson, H. M.: Macrosomia, cardiac hypertrophy, erythroblastosis and hyperplasia of islands of Langerhans in infants born to diabetic mothers. J. Pediat. *23:* 251, 1943.

Mollison, P. L.: Blood transfusion in clinical medicine. Blackwell Scientific Publications, Oxford. 1951.

Oettinger, L. and Mills, W. B.: Simultaneous capillary and venous haemoglobin determinations in the newborn infant. J. Pediat. *35:* 362, 1949.

Potter, E. L., Seckel, H. P. and Stryker, W. A.: Hypertrophy and hyperplasia of islets of Langerhans of foetus and newborn. Arch. Path. *31:* 467, 1941.

Van Slyke, D. D. and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. *61:* 523, 1924.

Walker, J. and Turnbull, E. P. N.: Haemoglobin and red cells in the human foetus. Lancet *II:* 312, 1953.

White, P. and Hunt, H.: Pregnancy complicating diabetes: Report of clinical reults. J. Clin. Endocrinol. *3:* 500, 1943.

White, P., Titus, R. S., Joslin, E. P. and Hunt, H.: Prediction and prevention of late pregnancy accidents in diabetes. Am. J. M. Sc. *198:* 482, 1939.

Received 9.2. 1954.

Barnkliniken
Karolinska Sjukhuset
Stockholm 60.

Acta Pædiatrica 43: 374—378. July 1954

CASE REPORT

Periarteritis Nodosa in an Infant of Three Months

by MICHAEL BOHMAN

From the Hospital for Contagious Diseases, Stockholm.
(Head: Justus Ström, M.D.)

Periarteritis nodosa (p.n.) occurs both in children and adults and available case reports refer to patients between 3 months and 78 years of age. In 1941 KEITH & BAGGENSTOSS put the total number of p.n. cases in children at 44. Their tabulation of 33 cases of p.n. reveals that signs of infection (fever and leukocytosis) were present most often. Fever occurred in 86 per cent, leukocytosis in 63 per cent, abdominal pains in 52 and "rheumatic pains" in 50 per cent. Signs of renal injury (40 %), asthenia (38 %), convulsions (38 %), tachycardia (34 %), anemia (34 %), purpura (27 %), urticaria (20 %) and hypertension (20 %), were fairly common but rarely palpable nodules, which were present in only 2 of the 44 cases.

Mention should be made of the relationship of p.n. to glomerular nephritis, Schonlein-Henoch's purpura, acute rheumatic fever and other diseases to which an allergic origin is attributed. I refer to papers by SPIEGEL, GAIRDNER and BERGSTRAND.

Formerly p.n. was thought to be fatal in all cases. Cases, however, have been published in which p.n. was diagnosed during life, the disease being chronic with long remissions, and cases in which the patient recovered. Owing to the increased attention now being paid to the disease, it is likely that it will be diagnosed in living subjects in an ever increasing number of cases.

Up to now, no causal therapy exists. Whether ACTH or cortisone constitutes any advance in the treatment cannot as yet be evaluated definitely.

Case Report

The patient was a boy of three months, admitted to the Hospital for Contagious Diseases, Stockholm, on February 16, 1949. Delivery had been normal, birth weight was 4,100 g and he had been fed on breast milk exclusively for one month. Then mixed feeding with cow's milk had been prescribed. However, he vomited after each feed of cow's milk, and on the advice of the child's physician who attributed the vomiting to an idiosyncrasy to cow's milk, he was given "Gerber's Baby Food", from December 1st, 1948. An elder brother had whooping cough, which set in about December 22. The patient was vaccinated against pertussis on January 2nd and 4th having injections of 1 and 2 cc respectively —i.e. large doses in proportion to the child's age. The injections were apparently given in the buttocks and the left upper arm, where inflammation and suppuration occurred and from which spontaneous discharge of pus took place. About the 6th of January he began to cough. The abscesses showed no further development after January 27th. The patient had attacks of coughing

ng with vomiting but no paroxysmal bouts. He had sulfa for some time without effect and until his admission to the Hospital he had a temperature of 39°–40° C. During the two days preceding admission he had penicillin procaine intramuscularly in the gluteals (50,000 I.U.).

On admission February 16th, 1949 the patient exhibited the following picture: normally developed for his age, had a high fever but was not obviously ill. Facial hue yellowish and pale. Tone and turgor normal. Edema of eyelids more pronounced on the right side. The fontanelle was the size of two finger tips. Slight tachypnea was present. Skin was slightly pale and icteric without exanthema. Above the right gluteal region there was a red area about the size of a child's palm, the soft tissues below it being infiltrated. Similar changes were seen in the left upper arm. Pharynx pale. Heart regular with rapid rhythm. Lungs: no abnormal sounds. The abdomen was soft. Small umbilical hernia. Spleen and liver not palpable. The blood showed marked anemia and slight leukocytosis with moderate preponderance of young neutrophils and no immature forms. The count varied somewhat during the course of the disease, relative to the repeated blood transfusions, but on the whole the values on admission remained constant. They were hemoglobin 7.1 g per cent. Red corpuscles 2.6 mill. white corpuscles 22,600. Diff.: rod nucleated 5, segment nucleated 71, eosinophils 2, basophils 0. Lymphocytes 21 and monocytes 1 per cent. The eosinophils varied between 2 and 7 per cent of the leukocyte counts ranging from 22,300 to 31,400. Urine: no albumin nor sugar; urine sediment normal. Bilirubin index (micro Meulengracht): February 20, 1:34; February 27, 1:20. Fragility of red corpuscles, February 24: total hemolysis with 0.20 and incipient hemolysis with 0.60 per cent NaCl. Bleeding and coagulation times not excessive. Prothrombin index 96.

In the course of the 16 days that the patient was treated at the hospital, the disease developed as follows:–

Throughout, the general condition was slightly affected but never alarmingly. His temperature varied between 38° and 39° C. Penicillin and sulfa drugs in large doses were ineffective. The patient was noticeably pale with an icteric tinge. The blood values were low and marked bilirubinemia was present. The patient's cough was at no time very alarming, and it improved, if anything, during the period in hospital. The patient was put on a diet of breast milk and thin gruel (cow's milk), and initially his weight increased favourably. He did not vomit and had no diarrhoea. After increasing steadily in weight, he began to lose rapidly what he had gained, so that from 6,000 g on February 26 he went down to 5,400 g on March 3, when he died.

After a few days palpation revealed a greatly enlarged, hardened liver (approximately at the level of the umbilicus) and the spleen could be felt at the arcus. On February 23 it was recorded that the patient was "on the whole better", less yellow and had a less enlarged liver which was palpable between the arcus and umbilicus. Also the edema of the scrotum and eyelids observed on admission was less. Nevertheless the temperature was still high and the diagnosis obscure. Roentgenography of the lungs on February 24 showed no abnormality. A sternal puncture on February 23 showed: "2 per cent myeloblasts and shift to the left, not definitely leukemic; toxic." ECG examination on March 3 disclosed signs of grave myocardial damage. From February 26 the patient deteriorated steadily and lost weight. After a subcutaneous infusion of 100 ml aminosol glucose the patient's condition deteriorated quickly, he became pale, peripherally cyanotic and cold, with rapid respiration and tachycardia. He died after a few hours on March 3rd 1949.

Necropsy. Incision in the left gluteal and sacral regions revealed in the subcutaneous

fat, under unchanged skin, a number of irregular, bean-sized, greyish-yellow necrot foci, some dry, others somewhat pasty. (Probably these abscesses originated from pe icillin-procain injections, the abscesses after the pertussis vaccine given in a rig buttock now being healed.) The main stems and larger branches of the coronar arteries were visible on the surface of the heart as greyish-yellow rather knotty cord apparently surrounded by inflammatory exudation. Some small, incised pieces r vealed swollen, knobly inner surfaces but no thrombosis. The *heart* might have be somewhat hypertrophic, weighed 90 g, and was somewhat dilated generally. A valves were thin and smooth and none of the cardiac cavities contained thromb Parts of the myocardium examined showed a slightly cyanotic-yellowish picture bu no apparent infarction or fibrosis. The *liver* was considerably enlarged, rather soft and weighed 600 g. The parenchyma was rich in blood and mottled red and yellow reminiscent mainly of stasis with fatty infiltration; perhaps some other small indistinc foci were included in the picture. The *suprarenal glands* were thin and macroscopicall normal. The *kidneys* appeared somewhat large and their surface was mottled by un equal, large, yellowish-white, red bordered foci up to the size of a navy bean, whic penetrated the cortex and had much the same appearance as infarctions. The marrow pyramids were cyanotic and the cortical parenchyma somewhat swollen.

Histologic examination: in many places the larger stems of the *coronary arteries* showed marked arteritic changes in various stages of development. Where the changes were fairly early the lumen was more or less completely occluded by intimal prolifera tion rich in fibroblasts and admixed with monocytic and inflammatory cells: lympho cytes, large monocytic elements, plasma cells and polymorphs, among them solitary eosinophils. The muscle fibres were in good condition and exhibited no marked necro biosis. Fibrinoid degeneration was not observed. The adventitia showed a similar, more or less extensive, inflammatory infiltration. Apparently the process was older in some arterial sections: the lumen was obliterated by a connective tissue mass and the wall hyalinized with scarcely perceptible muscular bundles. Here only the adven titia contained evidence of chronic inflammation rich in plasma cells. *Pericardium* showed a diffuse, subchronic inflammation with the same cell picture as above. *Myo cardium:* no fresh infarction or fibrosis could be demonstrated. Some of the larger coronary vessels were unchanged and arteriolar abnormalities were never observed. *Spleen:* the pulp exhibited considerable blood engorgement as well as infection with polymorpho-nuclear cells and numerous clusters of plasma cells. Here and there peri arteritic changes were seen. The intima of the arteries was unchanged, the media somewhat loosened with few inflammatory cells and no fibrinoid necrosis, and the adventitia showed an extensive inflammatory process with the same picture as that of the coronary arteries. *Liver* showed the picture of chronic stasis and fatty infiltra tion. No arterial changes demonstrated. *Kidneys:* moderate parenchymal congestive hyperemia. No diffuse glomerular changes. The infarctions showed the usual pictur of an anemic, young infarct with a hyperemic, hemorrhagic marginal zone. Arterit changes with intimal proliferation were observed at the apex of some infarcted area and so were inflammatory cells in different layers of the wall, but no fibrinoid necrosis. The larger arteries were unchanged in other sections of the kidneys. *Suprarenal glands* slight congestive hyperemia but no infarction. Pronounced arteritic changes of fairly young type were encountered in the fat adjoining one of the glands. *Lymph nodes* from different parts of the body showed very active growth centres. Abundan polymorpho-nuclear cells in the follicular margins. Moderate plasma cell reaction an sinus catarrh. *Subcutaneous abscesses:* normal epidermis. A subcuticular abscess wit

necrotizing granulation membrane. Nonspecific inflammatory picture with numerous plasma cells. No arterial changes.

In connection with the autopsy cultures were made from various organs according to the method of ADAMSON resulting in the growth of pathogenic micro-organisms:

	Escerichia coli	Staph. aureus	Entero-coccus	Strept. viridans	Gaffkya
1. Coronary artery	+	+	−	−	−
2. Gluteal abscessus	+	−	+	−	−
3. Lgl. submax.	+	+	−	+	−
4. Lgl. hil. pulm.	−	−	+	+	+
5. Spleen	+	+	+	+	−
6. Kidney	+	−	−	+	−
7. Liver	+	+	+	+	−
8. Lungs	+	+	+	+	−
9. Lgl. porta hepatis	+		+	−	+

Comment

From the clinical, histological and bacteriological point of view this seems to be a case of sepsis reacting with the same changes as are seen in periarteritis nodosa. There are also some allergical traits in the picture.

One subject for discussion in the case report here presented would appear to be whether the injected pertussis vaccine could have promoted the development of periarteritis nodosa in the patient or not. Assuming that the vaccine did play a role, it may have acted in different ways: (1) delayed allergic reaction to sterile vaccine, and (2) reaction to an infected vaccine. I have perused the literature on complications after pertussis vaccination. Among the complications the most frequent is encephalopathy of various types. GLOBUS & KOHN, for example, described two cases of postvaccinal encephalopathy. In one patient, a boy aged 8 years, who died of massive cerebral degeneration (found at autopsy) there were no arterial changes. I have been unable to find any cases of postvaccinal (pertussis) changes similar to p.n.

The latter alternative is rendered likely by the fact that bacterial cultures from different organs, produced a very rich and multitudinous flora. It would not be improbable, then, to assume that this flora originated in one of the abscesses mentioned in the clinical history as having erupted after the vaccination, so that the disease would be a reaction to the contents of these abscesses. It is however impossible to prove how the disease originated; one must be satisfied with the hypothesis that the postvaccinal abscesses could have played a part in the process. This assumption, however, is rendered less conclusive by virtue of the fact that the histological examination disclosed the presence of chronic changes, suggesting that the disease might have set in before the vaccine was given. The question of etiology must consequently be left unsolved, as so often happens in cases of periarteritis nodosa.

Summary

Description of a case, that of a 3 months old boy, in which the clinical picture was that of septic fever, local abscesses (after injections), mild jaundice, hepatic enlargement, and signs of myocardial injury. The diagnosis could not be made during life.

Necropsy and microscopical examination disclosed severe arteritic changes in several organs, particularly the coronary arteries and the arteries of the kidneys and suprarenal glands, where changes typical of p.n. were present. The lesions were partly of a chronic, sclerosing type (which might indicate that the disease set in during fetal life). Bacterial cultures post mortem gave a growth of pathogenic microorganisms from various organs. Since the disease became manifest clinically, after vaccination against pertussis, this etiology is discussed as well.

Périartérite noueuse chez un nourrisson de trois mois.

Description du cas d'un nourrisson de trois mois présentant le tableau clinique d'une infection, survenue après une vaccination contre la coqueluche. L'autopsie et les examens microscopiques montraient d'importantes lésions artéritiques dans plusieurs organes, et caractéristiques de la périartérite noueuse. Des cultures bactériennes faites post-mortem ont montré l'existence de micro-organismes dans divers organes. L'étiologie de l'affection est discutée.

Periarteritis nodosa bei einem 3 Monate alten Kinde.

Der Fall eines 3 Monate alten Knaben, bei dem nach einer Pertussisvaccination das klinische Bild einer Sepsis auftrat, wird berichtet. Die Obduktion und mikroskopische Untersuchung zeigte schwere für Periarteritis nodosa typische Veränderungen in verschiedenen Organen. Nach dem Tode angelegte Bakterienkulturen ergaben Wachstum pathogener Mikroorganismen in verschiedenen Organen. Die Frage der Ätiologie wird diskutiert.

Periarteritis nodosa en un lactante de tres meses.

Se comunica el caso de un niño de tres meses de edad, con un cuadro clínico septicémico, que apareció después de ser vacunado contra la coqueluche. La necropsia y el examen histológico revelaron manifestaciones arteríticas graves, típicas de la periarteritis nodosa, en varios órganos. Cultivos bacteriológicos post-mortem demonstraron desarrollo de microorganismos patógenos a partir de muestras de varios órganos. El problema etiológico es discutido.

References

1. Adamson, C.-A.: A bacteriological study of lymph nodes. Acta med. scandinav. *133*, Suppl. 227, 1949.
2. Bergstrand, H.: Morphological equivalents in poly-arthritis rheumatica, periarteritis nodosa, transient eosinophilic infiltration of lung and other allergic syndromes. J. Path. & Bact. *58*: 399, 1946.
3. Gairdner, D.: The Schoenlein-Henoch syndrome (anaphylactoid purpura). Quart. J. Med. *17*: 99, 1948.
4. Globus, J. H. and Kohn, J. L.: Encephalopathy following pertussis vaccine prophylaxis. J.A.M.A. *141*: 507, 1949.
5. Keith, H. M. and Baggenstoss, A. H.: Primary arteritis (periarteritis nodosa) among children. J. Pediat. *18*: 494, 1941.
6. Klein, S. P.: Periarteritis nodosa, study of chronicity and recovery, with report of two cases. Arch. Int. Med. *84*: 983, 1949.
7. Spiegel, R.: Clinical aspects of periarteritis nodosa. Arch. Int. Med. *58*: 993, 1936.

Received 11.8. 1953.

Johannesgatan
Stockholm C.

Acta Pædiatrica **43**: 379–385. July 1954.

Megaloblastic Anemia in Infancy

Megaloblastic Anemia Occurring in an Infant of a Mother Suffering from Pernicious Anemia of Pregnancy

by R. ZETTERSTRÖM and S. FRANZÉN

From the Pediatric Clinic, Karolinska sjukhuset, Stockholm

Nutritional anemias of a type morphologically resembling pernicious anemia in adults, have long since been reported in infancy: the best known being the so-called goat's milk anemia and the megaloblastic anemia seen in coeliac disease. The morphological resemblance to Addisonian anemia was noted by PARSONS and by VEENEKLAAS; the response to liver therapy by ROMINGER. On the basis of 25 cases ZUELZER and OGDEN in 1946 were able to show that megaloblastic anemia in infancy is a definite clinical entity. Since then, several cases have been published both from America and from Europe (AMATO, STURGEON). The anemia has been shown to respond not only to liver therapy but also to folic acid (10), or to citrovorum factor (8). Less often this type of anemia has responded to vitamin B_{12} but a few cases have been published, wherein dramatic improvement had followed administration of this vitamin (3). In many cases the anemia has developed from a purely nutritional basis such as occurs in deficiency states in artificial feeding, or when there have been prolonged periods of diarrhoea (11). In other cases, however, the etiology has been obscure.

The following case of megaloblastic anemia responding to vitamin B_{12} therapy is published since it appears to give good evidence for an etiology which has not been fully recognised hitherto.

A four months old boy, J. B., born 6.11. 51: the second child in the family. His birthweight was 2,880 g. During the pregnancy the mother had suffered from an anemia of unknown etiology, as treatment for which she had received a blood transfusion a few days before the expected date of delivery. When examined after birth the child showed no evidence of disease. From birth until admission to hospital the infant was entirely breast fed by the mother. The infant was followed up at a Child Welfare Center and seemed to develop quite normally during the first two months: at this time he suffered a mild upper respiratory infection, following which he failed to thrive, an increasing pallor was noted and there were periods of slight vomiting, the stools were however said to be normal. When four months old the infant was admitted to hospital because of severe anemia.

Physical examination on admission revealed a moderately sick child with extreme pallor but no jaundice. He was slightly hypotonic but relatively well nourished, with a weight of 5,100 g. There was slight craniotabes but otherwise the skeleton was normal. He had a mild pharyngitis but was afebrile, and clinical examination of the lungs showed nothing abnormal. A systolic murmur of the type found in anemia was present. The liver was palpable one cm below the costal margin: the spleen was palpable 3–4 cm below the costal margin, the surface was smooth and the consistency relatively firm. No other abnormalities detected.

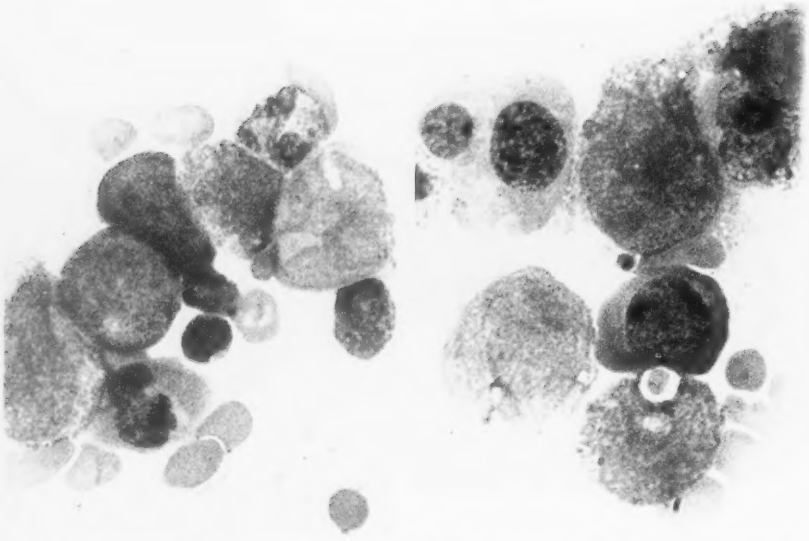


Fig. 1. Smear from tibial marrow of the child before treatment. Moderate degree of cellularity. No fat. Myelopoiesis-erythropoiesis ratio 5:3. Highly degenerative changes in the myelopoiesis with giant rod forms and hypersegmentation. The erythropoiesis completely megaloblastic.

Blood examination revealed a severe anemia, marked leucopenia and a moderate thrombocytopenia: Hb 3.4 g per 100 ml; red cells 970,000 per cmm; white cells 3,100 per cmm with only 11 % leucocytes in the differential count, the granulocytes showing degenerative changes. Platelets in two examinations were 72,000 and 36,000 respectively. Reticulocytes 1.5 %. There was marked poikilocytosis and polychromasia. Determination of red cell diameter showed increased spreading, the mean diameter being 7.2 microns. In the blood smear no definite macrocytes were noticed. Blood group 0 Rh(–). Coombs' test negative. Normal fragility of the red cells. Serum bilirubin was 0.89 mg per 100 ml. Prothrombin time normal.

Bone marrow biopsy showed typical changes of a megaloblastic dysplasia in the erythroid series: this is shown in Fig. 1.

Other investigations. The gastric juice showed minute amounts of free HCl after histamin stimulation. Roentgen examination of the skeleton revealed nothing abnormal.

Investigation of the mother. Because of her anemia during pregnancy, she was investigated after the child's admission to hospital. The blood showed Hb 12.0 g %, red cells 3.8 millions per cmm; white cells 2,600 with 52 % leucocytes in the differential count. Bone marrow biopsy, as is illustrated in Fig. 2, showed degenerative changes in the granulocyte precursors, typical of pernicious anemia, with only slight changes in the erythroid cells. The over-all picture was that found in healing pernicious anemia.

Treatment and Prognosis. Because of the child's critical condition on admission, transfusion of whole blood was given on the first day. Following transfusion, the

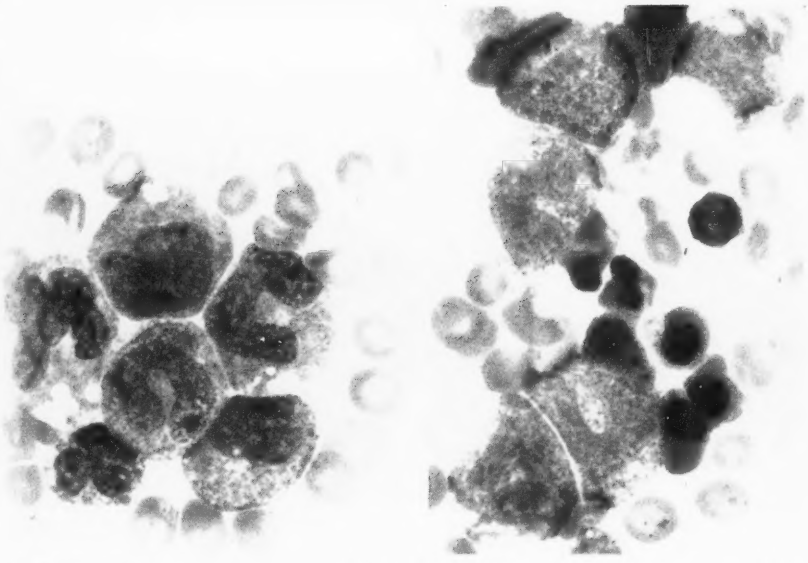


Fig. 2. Smear from sternal puncture of the infant's mother The preparation very rich in cells. M–E ratio 5 : 3. Highly degenerative changes in the myelopoiesis with giant rod forms and hypersegmentation. The erythropoiesis is normoblastic. The bone marrow picture is that of a pernicious anemia when in relapse.

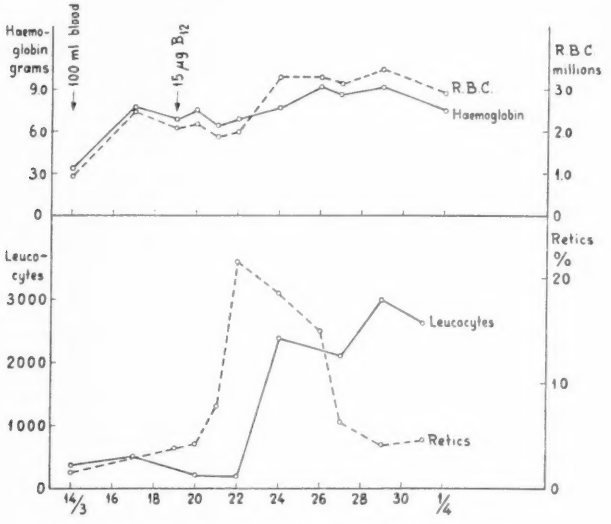


Fig 3. Effect of vitamin B_{12} on the blood values.

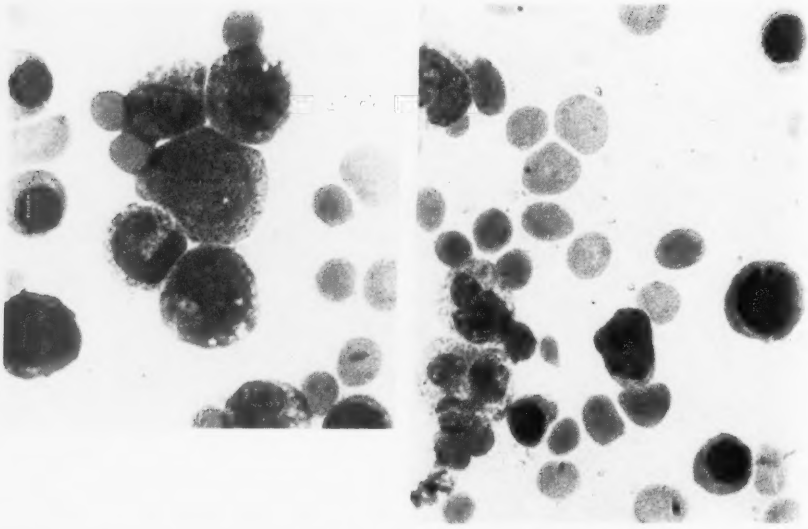


Fig. 4. Smear from tibial marrow 10 days after one injection of 15 µg B_{12}. The marrow preparation rich in cells. M–E ratio 3:2. The myelopoiesis shows only slight degenerative changes. The erythropoiesis is completely normoblastic.

blood values rose but decreased rapidly again. When the diagnosis of megaloblastic anemia was clear, a single dose of 15 µg of vitamin B_{12} was given intramuscularly. Within a few days of this single dose there was a dramatic response, as evidenced by the marrow pattern, the reticulocyte peak (up to 20 % reticulocytes) and the increase in the number of leucocytes. The weight began to increase as did the Hb content and the number of red cells: Fig. 3 shows the effect of vitamin B_{12} on the hematological values of the peripheral blood.

Fig. 4 shows the bone marrow pattern ten days after administration of vitamin B_{12}: as can clearly be seen the erythroid series is quite normal and in the myeloid series there are only slight degenerative changes.

A second injection of 15 µg of vitamin B_{12}, nine days after the first, gave no significant reticulocyte response nor did high doses of folic acid. The child was discharged from hospital four weeks after admission, in good condition and with practically normal blood values. On leaving hospital he was on a formula of cow milk complemented with fruit and vegetable.

Follow-up examinations during the year subsequent to hospitalisation showed no pathological findings, the blood values being quite normal and he never required further therapy.

Summary of the case history. A four months old boy, born of a mother suffering from pernicious anemia of pregnancy. He was entirely breast fed. After the age of two months he developed gradually increasing pallor and was admitted to hospital with marked anemia of the megaloblastic type. Dramatic response to a single dose of vitamin B_{12} (15 µg) No further therapy was required.

Comment

The case reported is, from the clinical and hematological findings, an authenticated instance of megaloblastic anemia of infancy with signs of disturbed formation of erythrocytes, granulocytes and thrombocytes. There was no histamin refractory achlorhydria, which occurs frequently in infants with megaloblastic anemia, but the values for free hydrochloric acid were extremely low. According to ZUELZER and RUTZKY the achlorhydria seems always to be transitory in nature.

Megaloblastic anemia in infancy is to be considered as a deficiency disease but the etiology is not the same in all cases. Many cases described have occurred in deficiency states due to artificial feeding, but others have occurred in the breast fed. Some are thought to have suffered from resorption difficulties due to severe gastrointestinal disorders (11). Most cases reported have responded to citrovorum factor or its precursor, folic acid, and the disease has therefore been considered to be a folic acid deficiency disorder. The etiology need not be the same in all cases, for in some instances deficiency in one or more factors, may be present. A few cases reported have responded best to vitamin B_{12} alone (3, 11); in most cases, however, vitamin B_{12} has failed to cause a satisfactory response.

In our case the prompt response following injection of vitamin B_{12}, as revealed by the marrow pattern and the reticulocyte peak, and the failure to obtain a further reticulocyte response to a high dose of folic acid, demonstrates that vitamin B_{12} was the missing factor. The etiology of such a deficiency, as the infant was breast fed, must lie in the mother's milk and it seems reasonable to assume that this deficiency was caused by the pernicious anemia of pregnancy from which, according to the bone marrow pattern, she was suffering. Unfortunately no determinations of the concentrations of folic acid and vitamin B_{12} in the mother's milk were made. As the majority of AMATOS' cases were breast fed, the cause of the megaloblastic anemia, must in some of his cases, have been a deficiency in the milk. One cannot decide, however, whether his cases were suffering from a deficiency in folic acid or vitamin B_{12}, since the anemia was cured by liver therapy which supplies both the citrovorum factor and vitamin B_{12}. Quite recently ZUELZER and RUTZKY have reported a case in a breast fed infant whose mother was said to have been suffering from anemia during pregnancy; in this case synthetic citrovorum factor failed to cause complete remission, the marrow becoming quite normal, however, immediately after therapy with vitamin B_{12}. Of the great number of cases observed by ZUELZER, this is the only one which failed to improve after treatment with citrovorum factor or its precursor, folic acid.

Vitamin B_{12} might be the missing factor in megaloblastic anemia of infancy, though much less often than citrovorum factor. This etiology seems to occur especially in breast fed infants of mothers suffering from pernicious anemia of pregnancy. Citrovorum factor and vitamin B_{12} are both concerned in nucleic acid synthesis, neither factor being able to replace the other (9), and the deficiency of ascorbic acid, often observed in this disease (2), points to the important role played by vitamin C in the pathogenesis. This interaction seems to depend on the fact that ascorbic acid acts as a coenzyme in the mechanism which transforms folic acid to citrovorum factor.

Summary

1. A case is described of megaloblastic anemia in a four months old breast fed infant, whose mother was suffering from pernicious anemia of pregnancy. The anemia responded promptly to vitamin B_{12}. There was no further therapeutic effect from folic acid, a fact indicating that vitamin B_{12} was the missing factor in this case.

2. Infants born of mothers suffering from pernicious anemia of pregnancy should be controlled with regard to megaloblastic dysfunction of the bone marrow.

Les anémies mégaloblastiques de l'enfance. Sur un cas d'anémie mégaloblastique chez le nourrisson d'une mère ayant présenté une anémie pernicieuse de la grossesse.

Un cas d'anémie mégaloblastique chez un nourrisson de 4 mois, nourri au sein et dont la mère avait présenté une anémie pernicieuse de grossesse, est rapporté. L'anémie se répara très vite par la vitamine B_{12}. Un traitement ultérieur par l'acide folique fut sans effet, fait significatif que la vitamine B_{12} était bien le principe absent dans ce cas. Les enfants nés de mères ayant présenté une anémie pernicieuse au cours de la grossesse doivent être examinés en recherchant un dysfonctionnement mégaloblastique de la moëlle osseuse.

Megaloblastenanaemie im Säuglingsalter. Megaloblastenanaemie bei einem Kinde, dessen Mutter während der Schwangerschaft an einer perniziösen Anaemie litt.

Es wird der Fall eines Kindes beschrieben, dessen Mutter unter der Schwangerschaft an perniziöser Anaemie litt. Die perniziöse Anaemie wurde prompt durch Vitamin B_{12}-Zufuhr beeinflußt. Folinsäure hatte keinen Effekt, eine Tatsache, die bestätigt, daß Vitamin B_{12} der fehlende Faktor war. Neugeborene, deren Mütter während der Schwangerschaft an perniziöser Anaemie erkrankt waren, sollten im Hinblick auf eine megaloblastische Dysfunktion des Knochenmarkes kontrolliert werden.

Anemias megaloblásticas en la primera infancia. Anemia megaloblástica en un lactante cuya madre padecía de anemia perniciosa del embarazo.

Se describe un caso de anemia megaloblástica en un lactante alimentado con leche materno, cuya madre sufría de anemia perniciosa del embarazo. La anemia cedió rápidamente al tratamiento con vitamina B_{12}. No hybo ulterior efecto terapéutico del ácido fólico, hecho que indica que en este caso se trataba de una carencia de vitamina B_{12}. Los niños nacidos de madres con anemia perniciosa gravídica debieran ser controlados en relación a la posibilidad de una disfunción megaloblástica de su médula ósea.

References

1. Amato, M.: Rilievi anamnestico-clinici, ematologici e biochemici e considerazioni patogenetiche su 25 casi di anemie ipercromiche megaloblastiche observate in bambini della prima infanzia. Pediatria *54:* 71, 1946.
2. May, C. D., Nelson, E. N., Lowe, C. W. and Salmon, R. J.: Pathogenesis of megaloblastic anemia in infancy. An interrelationship between pteroylglutaminic acid and ascorbic acid. Am. J. Dis. Child. *80:* 191, 1951.
3. McPherson, A. Z., Jonsson, U. and Randles, R. W.: Vitamin B_{12} therapy in megaloblastic anemia of infancy. J. Pediat. *34:* 529, 1949.
4. Parsons, L. G.: Studies in anemia of infancy and early childhood. Arch. Dis. Childhood *8:* 85, 193
5. Rominger, E., Meyer, H. and Bomskow, C.: Anämiestudien am wachsenden Organismus: Über die Pathogenese der Ziegenmilchanämie. Ztschr. ges. exper. Med. *89:* 786, 1933.
6. Sturgeon, P. and Carpenter, G.: Megaloblastic anemia of infancy. Response to vitamin B_{12}. Blood *5:* 458, 1950.
7. Veeneklaas, G. M.: Über megalocytäre Mangelanämien bei Kleinkindern. Folia haemat. *65:* 30 1942.
8. Woodruff, C. W., Peterson, J. C. and Darby, W. J.: Citrovorum factor and folic acid in treatment of megaloblastic anemia in infancy. Proc. Soc. Exper. Biol. & Med. *77:* 16, 1951.

9. Woods, D. D.: The function of folic acid and related growth factors in the metabolism of microorganisms. Symposium sur le métabolisme microbien. II[e] congrès international de biochimie. Paris 1952.
10. Zuelzer, W. W. and Ogden, F. N.: Megaloblastic anemia in infancy: A common syndrome responding specifically to folic acid therapy. Am. J. Dis. Child. *71:* 211, 1946.
11. Zuelzer, W. W. and Rutzky, J.: Megaloblastic anemia of infancy. Advances Pediat. *6:* 243, 1953.

Received 29.10. 1953.

Barnkliniken
Karolinska sjukhuset
Stockholm 60.

Acta Pædiatrica 43: 386—392. July 1954

SUMMARY OF SUPPLEMENTS

La maladie des griffes du chat (Cat Scratch Fever)

by R. DEBRÉ and J.-C. JOB

Acta Pædiat. 43, 1954, Suppl. 96

Following the observation, during more than 10 years, of subacute suppurating adenitides after cat scratches, we managed since 1947 to identify them with certainty with the help of the specific intradermal reaction conceived by Lee Foshay. We described them first, in association with M. LAMY, M. L. JAMMET, L. COSTIL, and P. MOZZICONACCI, in January 1950, under the name of Cat-scratch fever (Maladie des griffes de chat). Shortly afterwards, many cases were reported in France, Switzerland, the U.S.A. and a large number of countries, thus conforming, widening and completing our first findings. A description is given here of the disease on the basis of our 80 cases and of the whole of the published cases, the number of which is well over 300.

Cat scratch fever is found throughout the world, under all climates and in all age sections. A cat is the usual vector and inoculating agent: a contact with one or several cats was definitely established in 83 % of the cases. In 54 % the disease was inoculated by a cat scratch, and in 6 % by a cat bite, whereas only 13 % of the patients developed a lesion around an excoriation due to a thorn, to a metal or wood fragment, or insect sting. The existence of familial epidemics, at the origin of which a cat living with the family was always found, further substantiates the value of these statistical data. Nevertheless the transmission of the disease is only incompletely known: 17 % of the patients had no contact with a cat and 27 % failed to remember an inoculating trauma. It seems that the cat's transmitting capacity does not exceed several days or weeks, himself being not affected. The source of the virus, its natural reservoir have not been discovered. Nevertheless there must exist a reservoir, as suggested by our report of an endemic of 1 cases transmitted during 5 years by the cats of a small town in the vicinity of Paris.

Although cat-scratch fever is certainly of infectious nature, the causative agent has not so far been identified. MOLLARET, REILLY, BASTIN, and TOURNIER, have reported that the disease can be transmitted to men and monkey

and that it may inconstantly give a complement deviation with the antigen of lymphogranuloma venereum. These authors demonstrated the existence in monkeys and sometimes in men of cellular inclusions bearing evidence, in their opinion, of the existence of a virus; we failed to discover and to study these inclusions in our sections of human lymph nodes. We do not think that it is permitted to establish a full relationship with the viruses of the ornithosis-lymphogranuloma venereum group, because of morphological differences and chiefly of the failure of inoculations on embryonic eggs. We report the results of our investigations carried out with ganglionic pus and nodes taken unfortunately fairly late; the cultures on various media, the inoculations on tissue cultures and on the yolk sac of incubated eggs and ultimately to various rodents and monkeys failed. On the contrary, the inoculation of crushed nodes to rodents treated with cortisone enabled us to obtain cutaneous lesions without adenopathies, transmissible in series of animals; their specificity is not unquestionable.

The typical form of Cat-scratch fever associates a cutaneous lesion of inoculation, a regional adenitis and general manifestations. The duration of incubation ranges from two to six weeks. Several nodes of a same group, most often the axillary one, are involved, or sometimes two connected groups; the adenitis is of very variable volume, either solid or fluctuating; it suppurates in 50% of the cases. The inoculation lesion is to be seen in one half of the patients, under the aspect of a small macula or papula, which is often precocious and transient but may appear again when the adenitis is formed. At this stage, a slight attack of fever lasting about ten days, is commonly seen. The course is always benign. The adenitis either disappears spontaneously or the pus is evacuated through a fistula possibly simulating tuberculosis; anyway, recovery is complete within several weeks or months, a protracted course being very uncommon.

Laboratory examinations are necessary and an unquestionable diagnosis must be based on a positive intradermal reaction. The injection of 0.1 ml of diluted pus induces the formation, 3 or 4 days later, of a pinkish papula with a diameter of 6 mm or more, and sometimes a focal or systemic reaction. This test is specific and lasting; but some failures require the use of various different antigens. The complement deviation test is not specific and sometimes not contributory. The examination of the sterile pus or of ganglionic smears, obtained by punctures, is of diagnostic value, as well as a biopsy performed in several cases. The blood count is not much modified. On the basis of all these findings, it is possible to differentiate catscratch fever from other subacute adenitides. In the absence of inoculations cutaneous lesions, adenitides due to common pyogenic organisms, tuberculous adenitis, Hodgkin's disease and lymphogranuloma venereum are to be dis-

carded in the first place; diagnosis with tumors of the lymphatic gland, acquired toxoplasmosis and giant follicular lymphadenopathy is more uncommon. If there is an adenitis associated with a skin lesion, tularemia and other pasteurella infections, soduku and mycoses will be discussed. If there is a polyadenitis, infectious mononucleosis, brucelloses and sarcoidosis will be considered.

Several clinical forms of cat-scratch disease are known at present. There are symptom-free forms, protracted forms, so called "pseudovenereal" inguinal forms, forms with superinfection of the adenitides by tubercle bacilli. A maculous eruption or true erythema nodosum may accompany the adenitis. Especially interesting are the ectopic forms of the disease: oro-pharyngeal (associating tonsillitis or a pharyngeal abscess with a cervical adenitis); palpebral; conjunctival with pre-tragal adenitis assuming the aspect of Parinaud's conjunctivitis; mesenteric (abdominal adenitis simulating appendicitis); thoracic (with involvement of the mediastinal nodes or primary atypical pneumonia). The most special forms are those with neuro-meningeal accidents: encephalitis, myelitis, nevritis and meningitis. The number of cases, in which cat-scratch fever is to be suspected and the intradermal reaction resorted to, is ever and ever increasing. The diagnostic criteria of these forms are given with accuracy and it is reminded that in these forms, too, a cat is the usual carrier of virus.

The pathological examination of a cat-scratch fever adenitis usually shows several nodes of different volume, circumscribed by loose periadenitis and containing areas of suppuration of variable size. The microscopic study shows the disappearance of the normal node pattern, which is replaced by an inflammatory granuloma with areas of reticular hyperplasia with large clear cells and other areas infiltrated by round cells, polymorphonucleaus and some plasmocytes; the granuloma is later the seat of necrotic foci which melt into pus. Typically, there is a follicular structure: lympho-plasmocytic peripheral circle, area of epithelioid cells "en palissade" scattered with Langhans giant cells, necrotic centre. Stress is laid on the very marked reticular and endothelial hyperplasia and on the very early appearance of sclerosis at the periphery of the granuloma. This histological pattern is not specific of cat-scratch fever and is related to aspects found in other ganglionic granulomas (tuberculosis, Hodgkin's disease, sarcoidosis, lympho-granuloma venereum, infections and mycotic adenitis). The skin lesion of inoculation is made of a granuloma similar to that of the node, with the same reticular hyperplasia.

The action of treatment is difficult to appraise because of the usual very benign course. A puncture of the node permits the removal of the pus and is the first treatment to carry out. Antibiotics should be used if the adenitis

or fever outlasts the puncture; aureomycin induced the cessation of the fever and accelerated the recovery of the adenitis in nearly all treated cases. Other authors obtained similar results with terramycin, chloramphenicol and erythromycin. If the adenitis is not cured by antibiotics, surgical removal may be indicated. Antibiotics will be given in all ectopic or complicated forms.

Studies in Diabetes Mellitus

by GUNNAR ENGLESON

Acta Paediat. 43, 1954, Suppl. 97

Factors considered of primary importance in the development of late complications of diabetes were studied in an adult series of 217 patients, treated at the medical department Växjö Hospital and in a childhood series consisting of 42 juvenile diabetics treated at the pediatric department University of Lund. Both series were on a free diet.

Attention was directed mainly to the importance of diet and to problems bearing on liver metabolism and endocrine function and the results are accounted for against the background of literature studies of earlier investigations in this field.

The observations of interest may be summarized as follows:

1. Of the Växjö series, which consisted of patients in whom diabetes had occurred before the age of 40 years, the following late complications were noted after 5—25 years of duration of diabetes: Nephropathy in 65 per cent, retinopathy in 60 per cent and hypertension in 65 per cent. Nephropathy was practically always the first of these late symptoms.

Of the patients who had had their diabetes for more than 10 years, only 7 ($6^1/_2$ per cent) were free of vascular complications.

The Kimmelstiel-Wilson syndrome was diagnosed on clinical grounds in 2 cases and in one third of them the diagnosis was confirmed *post mortem*. The serum hexosamine was found often to be increased, especially in the presence of vascular lesions.

2. Of the Lund series (19 boys and 23 girls) the liver parenchyma was found to be involved in 40 per cent.

Typical of these liver complications is that they appear about 5 years after the onset of diabetes, that they are fairly often (about 30 per cent) seen in combination with moderate retardation of growth and sometimes

(about 20 per cent) with co-existent or subsequent vascular complications in the form of nephropathy and/or retinopathy.

Endocrine function studies in the Lund series suggested that a primary endocrine non-pancreatogenic form of diabetes is rare and that the functional patterns of the adrenal cortex during ketosis or "stressful life situations" readily changes.

The observations described above suggest the following conclusions:

1. The development of long-term diabetes is influenced not only by duration of the diabetes but also by any impairment of liver function and by endocrine factors probably mediated via the adreno-hypophyseal axis and by stressful life situations.

2. The disturbed liver function and endocrine homeostasis of the body is ascribable or at least favoured by unrestricted diet.

3. Dietary restrictions should be observed in the management of diabetes, especially as a prophylactic measure against long-term diabetes.

The Resistance of Red Cells in Vitro

by STIG SJÖLIN

Acta Paediat. 43. 1954. Suppl. 98

The main object of the investigation was to study some physical properties of the fetal red cells in order to find out whether, or to what extent, fetal red cells differed from adult red cells. A short survey of the properties of adult and fetal red cells with special reference to the characteristic shape and hemoglobin differences was first given.

The *osmotic resistance* was studied in buffered, hypotonic NaCl solutions (pH 6.8; temp. $+4^{\circ}$ C), and the amount of liberated hemoglobin was used as a measure of the degree of hemolysis. Percentage hemolysis curves were thus obtained. A characteristic variation of the osmotic resistance at different ages was observed. The majority of the red cells of young fetuses showed a lower resistance than the red cells of cord blood of full-term infants. A continuous increase in resistance towards the cord blood values was noticed during the fourth and fifth months of gestation. The mean osmotic resistance of cord blood and adult blood did not differ. The span of hemolysis, however, was greater in cord blood, the resistant cells especially being more numerous than in adult blood. During the whole childhood the resistant cells were more numerous than in adult blood. The greatest number of resistant cells

was found during the first days of life and the end of the first year of life. During the first six months of life the resistance distribution was skew, thereafter it was practically normal. At about puberty a definite shift to the adult red cell type seemed to occur.

Special attention was paid to the methodological problems, to the statistical treatment of percentage hemolysis curves, and to the significance of the osmotic resistance test. The changes in osmotic resistance were interpreted as depending, at least partly, on variations in the red cell shape. It was found impossible to draw any definite conclusions from the osmotic resistance as to the age or to the in vivo survival of different normal red cells. The oldest cells, however, seemed to belong to the osmotically most resistant part of the red cell population. The changes in osmotic resistance were regarded as indications of variations in the composition of the red cell population or in the red cell environment.

The rate of volume increase of red cells in buffered, hypotonic NaCl solutions (pH 7.0; temp. +20° C) was measured photometrically and was regarded as a measure of the *rate of entrance of water* into the red cells. The *permeability coefficient* of water was calculated from these experiments. A greater value was found for adult red cells than for cord blood red cells, 22.1×10^{-3} cm sec.$^{-1}$ and 11.7×10^{-3} cm sec.$^{-1}$ respectively. The difference was interpreted as depending on differences in the membrane of the two types of cells. The obtained permeability coefficient of adult red cells was discussed in relation to the present conception of the red cell membrane structure. The information obtained by the permeability studies was found to be in good accordance with the opinion derived from earlier chemical and electron microscope investigations. Because different methods gave varying permeability coefficients for the same blood, methodological problems concerning the determination of the permeability coefficient were also treated.

When a blood sample is subjected to a standardized *mechanical trauma*, some red cells will burst and hemolyse. The percentage of undestroyed red cells was regarded as a measure of the mechanical resistance. A decreased mechanical resistance was found at birth and during the first two to three months of life. This greater vulnerability may indicate a shorter in vivo survival of the cord blood red cells, but there is no proof of such a presumption. With regard to normal red cells the mechanically most resistant cells also seemed to be the osmotically most resistant ones.

During *cold storage* (+4° C) of whole blood the glycolytic metabolism of the red cells is minimized. As a result of the failing metabolism the red cells swell, their osmotic resistance decreases and they lose potassium and gain sodium in accordance with their diffusion coefficients and concentration gradients. Judging from changes in the osmotic resistance and in the cation

permeability, the cord blood red cells equilibrated their cations faster than the adult red cells. The difference was attributed to membrane differences between the two types of cells.

During *storage at + 37° C* glycolysis at first proceeds at the in vivo rate, and the normal in vivo concentration gradients of the cations are maintained. Judging from the potassium loss curves during storage at + 37° C the metabolism of the cord blood red cells seemed to fail earlier than that of the adult red cells. After the metabolic failure it was not possible to prove any difference in the rate of cation equilibration between cord blood and adult red cells.

Acta Paediatrica 43: 393—397. July 1954

Proceedings of the Section for Pediatrics and Shool Hygiene of the Swedish Medical Society

Meeting, April 9, 1954

L. Hofman-Bang: **Diabetic coma in a three weeks old infant.**

There was nothing unusual in the pregnancy or parturition. The child had been healthy until the day before admission. He then fell ill with typical signs of diabetic coma. On examination, loss of conscience, dehydration, shock, and convulsions. The nutrition was rather bad and there was a marked hepatomegaly. Blood sugar 844 mg%, acetonuria. Improvement after re-hydration and insulin, of which 44 units in 6 injections were given during the first day. Cerebrospinal fluid normal. EEG revealed leftsided frontocentral focus. X-ray of the skull normal. In previously described cases of diabetes in infants below one month of age acetonuria has not occurred.

G. Flyger: **Some views upon the surgical treatment of internal hydrocephalus.**

A review was given of various types of congenital internal hydrocephalus and the possibilities of neurosurgical treatment were discussed. From the diagnostic point of view a subdural haematoma should first be excluded by subdural tap. Next it is necessary to determine if a communicating hydrocephalus is present or not by cytochrom injection in one of the lateral ventricles and a subsequent lumbar tap. For an exact diagnosis encephalography in addition to ventriculography is necessary. The cases should be operated on as soon as possible, before cerebral atrophy has occurred. Mentally normal children in good condition should be operated upon. In communicating hydrocephalus an extirpation of the plexus is made (high mortality rate), or a coagulation of the plexus, which seems to give more satisfactory result. In the non-communicating hydrocephalus frontal or occipital ventriculo-cisternostomy is made. Collaboration between the neurosurgeon and the paediatrician is of great importance.

Discussion: *B. Vahlquist* has seen a child with initial progressive hydrocephalus that has spontaneously recovered. — *G. Flyger:* Such spontaneously recovered cases are usually due to perforation of a non-communicating hydrocephalus into the subdural space. The operation should not to be postponed although such cases may occur.

I. Werner: **On secretin and pancreozymin as a means in the diagnosis of pancreatic diseases.**

Report of preliminary studies on pancreozymin- and highly active secretin-preparations. Secretin tests were performed in the ordinary way, and in addition a pancreozymin test has been made. As the secretin is effective solely on the fluid- and alkali excretion and the pancreozymin specifically stimulates the enzyme excretion of the pancreas, a combined test should be of greater value than the secretin test alone.

A. Dahlström and *E. Odelstierna:* **Case of lead intoxication?**

A diagnostically uncertain case of a 10 months old infant with convulsions. Th findings on examination made lead intoxication suspect on account of some bas philic granulated blood corpuscles, coproporfyrinuria, roentgenological density of th metaphyses and a pathological EEG. These findings rapidly became normal. Lea intoxication is, however, in spite of these findings considered not likely because n exposure in the previous 40 days before the first symptoms started could be demo strated and no lead excretion could be demonstrated in the urine.

Discussion: *R. Berfenstam* mentions the new versenat drug that is of advanta in comparison with BAL, because it forms atoxic and stable compounds with heav metal salts.

E. Hagberg: **Tuberculin reaction in infants of tuberculous mothers.**

In 191 newborns, BCG-vaccinated and isolated after birth from their tuberculou mothers, the time of onset of tuberculin sensitivity was controlled by tests in 2—3 weeks' intervals, partly performed with BCG-tuberculin, partly with Old Tuberculin. BCG-tuberculin gives earlier and more distinct reactions. As control group 9,000 infants of healthy mothers were used. In this control group 86.6 % were positive after 5—6 weeks, 90.5 % after 7—8 weeks, and 98 % after 9—10 weeks. The corre sponding figures for the group of infants of tuberculous mothers are 26.1 %, 46.0 % and 59.5 %, respectively. This result is especially surprising as in the latter group many of the children received double dose of BCG-vaccine and some of them had even to be revaccinated. If one waits a sufficiently long time, all these children of tuberculous mothers become tuberculin positive. Desensitization caused by the re peated tuberculin tests did not occur. The results are in favour of some intra-uterine, passively transmitted factors, possibly of antibody nature, which during the first 2—3 months interfere with the BCG-vaccine.

Discussion: *S. I. Rolloff:* Similar examinations had been made and the results of the speaker could be verified. In addition the tuberculous process of the mother had been evaluated in order to investigate if there was any relationship between the activity and extent of the tuberculous disease during pregnancy and the tuberculin reaction of the infant after BCG vaccination. It was found that the number of positives were evidently lower in a group where the tuberculous process of the mother during preg nancy was active than in a group where the process had been evaluated as inactive or healed. It was very evident that the incidence of positive reactions was smaller among infants of tuberculous mothers than among the infants whose father had tuber culosis. In only one of fifteen examined infants of tuberculous mothers antibodies according to Middlebrook-Dubos could be demonstrated. — *A. Wallgren:* In experi ments on animals passively transferred cells from tuberculin positive animals can produce passive tuberculin sensitivity in tuberculosis-free animals for a duration of about 2—3 months. — *K. Kaijser:* Is it better to postpone the BCG-vaccination in these infants in order to avoid the interference? Do you use BCG tuberculin routinely?

E. Hagberg: The effect is probably not more rapid of one waits with the vaccination. BCG tuberculin is soon going to be distributed by the State Bacteriological Laboratory.

A. Wallgren: Certain persons do not react to BCG-vaccination with tuberculin sensitivity, but in other ways it may be shown that they are immune. When I tried 20 years ago, to perform BCG-vaccination in newborns, we used only newborns o

tuberculous mothers. I stopped this procedure because I could not get any positive reactions within a reasonable length of time. Some years later the experience from other quarters showed that newborns in general are reacting to BCG. — *B. Vahlquist:* The Schick reaction in infants may be negative although no antibodies can be shown serologically, which indicates an especial mode of reaction in the cells of the infants. That the tuberculin reactions generally turn out later than in older children after BCG-vaccination may be due to the same mechanism. Both these factors may have the same influence in both groups demonstrated by Hagberg. The titer of passively transmitted antibodies decreases according to an exponential curve. — *E. Hagberg:* It is very seldom that BCG-vaccinated children remain negative to BCG tuberculin.

S. I. Rollof: How does the BCG tuberculin test behave in virulent infections? — *E. Hagberg:* It has not been studied.

Meeting, May 29, 1954

K. Fichtelius: **Erythremia? in a newborn child.**

A newborn full term infant displayed widely distributed petecchiae and enlargement of liver and spleen. Two weeks before delivery the mother had suffered from an infectious disease of unknown origin. On the third day of life the infant had fever, after one week it died although transfusion and treatment with antibiotics and cortisone had been given. In the blood there was a reduction of the number of red blood corpuscles with an increase of normoblasts, of which many were immature types. There was a thrombocytopenia, a decreased fibrinogen content and a decreased retraction of the clot with a decreased albumin/globulin ratio. Blood culture negative. Bone marrow showed a dominating erythropoiesis with polyploidy and absence of transitional stages; a hiatus erythremicus. The myelopoiesis was depressed, the megakaryocytes evidently reduced. Also the extramedullary erythropoiesis showed pathologically a marked dominance of oxyphile erythroblasts and polyploidy. With great probability there was an erythremic leukemia.

(Will be published elsewhere.)

Discussion: *B. Vahlquist:* The diagnosis is not altogether evident but probably it was an erythremic leukosis. Congenital cases have not been described before. In differential diagnosis sepsis transmitted from the mother's infectious disease may be discussed.

S. Edlund: **Hereditary vascular collagenous disease.**

A boy, 4 years of age, was treated on several occasions for a hemorrhagic diathesis, manifested principally by subcutaneous bleedings after insignificant traumata. No enlargement of liver or spleen. Bone marrow showed some increase of the lymphocytic elements; the ascorbic acid content of the serum was decreased; otherwise the hematological data were normal. Biopsy showed pathological distended vascular lumina in the subcutis and an abnormal collagen. The father of the patient had had spontaneous rupture of his Achilles tendon and had had skin bleedings and had died from retroperitoneal haemorrhage. It is maintained that there was a hereditary disturbance of the collagenous tissue and due to this the vessels were pathologically distended and fragile.

K. H. Schäfer **(guest),** ***Hamburg:*** **Roentgenological studies in children with relapsing abdominal pains.**

Five hundred cases of relapsing umbilical colic were carefully investigated by means of contrast roentgenography. There were surprisingly many cases of ventricular ulcers and duodenal ulcers. In 1953 there were in all 13 cases of ulcer. In some of these there were symptoms typical of ulcer. In other cases gastro-duodeno-jejunites were found. Not infrequently abdominal lymphoma were demonstrated, some of them probably of tuberculous origin, others unspecific, which by compression had obstructed the lumen of the intestine. Other findings were trichocephalus, ascaris and taenia helminths. In addition there were local spasms of the small intestine and the colon. A site of predilection of roentgenologically demonstrable changes was the ileocaecal region, where lymphoma, swollen ileocaecal valvules, chronic appendicites, mobile caecum and, above all, terminal ileits were diagnosed. Every fourth examined child displayed an "ileitis terminalis catarrhalis". The great frequency of pathological findings stresses the importance of careful roentgenological examination in cases with symptoms of umbilical colic.

Discussion: *B. Vahlquist:* Has any especial roentgenological technic been employed? — *K. H. Schäfer:* Now we give the contrast perorally, earlier it was given retrogradly. The peristalsis promoting barium contrast preparations reduces the time of examination to 3 hours. — *F. Karlström:* In a children's ward with 50 beds there were 8 cases of gastric or duodenal ulcerations over a period of 2 years. — *K. H. Fischer:* There must be a certain selected material in the clinic in Hamburg with its 226 beds. 1952 there were 4 cases of ulcerations, 1953 13 cases, 1954 6 cases. — *A. Wallgren:* Although we almost always examine by means of X-rays cases with symptoms of umbilical colic, we very seldom get any positive results according to our experience. Terminal ileites have never been seen, perhaps depending on a unsatisfactory technic. The symptoms of umbilical colic disappear often when the children are admitted to hospital, which makes it difficult for a roentgenologist to demonstrate any spasm of the intestines. — *F. Knutsson* stresses the difficulty of differentiating roentgenologically between a true thickening of the ileocaecal valvule from a compression due to enlarged ileocaecal glands.

M. Pehrson: **The consumption rate of infants upon various milk formulas.**

In 16 infants, aged 1 – 6 months, the consumption rate of breast milk was determined and compared with thin gruels made from dry milk preparations of different types. The amount consumed was determined every third minute. The consumption time of dry milk preparations was somewhat shorter than for breast milk. On the other hand, the difference in the consumption rate between the sweet and the half sweetened dry milk type was very small.

Discussion: *A. Wallgren:* Why was the thin gruel not made from fresh cow's milk as we usually do? Dry milk preparations are not necessary in our country. — *G. Jacobsohn* recommends the use of fresh cow's milk. — *B. Vahlquist:* There is a bad milk hygiene in some places in our country and a simplified preparation of the dry milk mixtures indicates their use. — *P. Karlberg:* One avoids individual variations by statistically reckoning the differences between the consumption rate for each individual child.

I. Nordbring: **Immune globulins in colostrum.**

Preliminary results of paper electrophoretic analyses of certain protein components of the colostrum. The colostrum before and a variable time after parturition was examined. The analysis was made after removing fat and casein and the remnant was concentrated by dialysis. Post partum the electrophoretically slowly migrating immune globulines are decreased and the principal component is constituted by beta lactoglobulines. Rapidly migrating small fractions of albumins are also seen. Electrophoretic diagrams of serum were compared with milk after 4 months' lactation. The electrophoretically principal component of milk corresponded with the $beta_1$- and $beta_2$-globulins of the serum. The antibody content is analysed in colostrum and compared with serum in 72 cases. As to AST and ASTA these antibodies showed very low titres already in the first-day colostrum, on the fourth day they could no longer be shown.

A. Killander: **Serum-B_{12} in acute and chronic leukemia.**

The concentration of serum B_{12} has been examined microbiologically by means of Euglena gracilis var. bacillaris, according to a method described by Ross, with the difference that the growth was measured photometrically by determining the amount of extracted chlorophyll. In chronic myeloid leukemias the serum concentration of B_{12} is very high (8—35 times the mean value of a normal material); this was illustrated in 7 seven cases, of which 3 were children. This result is in contrast to other types of leukemia. This may be due to the more mature cell picture in chronic myeloid leukemia, in contrast to the changes in acute leukemia. High values have also been found in some cases of cirrhosis of the liver and in diabetes mellitus. Of interest in this connection is the leucopenia in untreated pernicious anemia and records of exacerbations of some leukemias in connection with B_{12} treatment.

BOOK REVIEWS

Alan Moncrieff: **Child Health and the State.**

Oxford University Press, London, 1953.

In this small volume (48 pages) the well-known British professor of Child Health at the University of London has collected his three Newsholme Lectures dealing with the responsibility of the Community, State and Parents for the welfare of children in Great Britain. The title of the lectures are: Infant Welfare, School Health, and The Deprived Child. Although the book is probably of most interest for the British, readers in other countries will get much valuable information and many important suggestions for the development of the welfare of children.

H. Michal-Smith: **Pediatric Problems in Clinical Practice. Special Medical and Psychological Aspects.**

Dr. Michal-Smith is a child psychologist in New York. Together with 12 other American pediatricians, child psychologists and child psychiatrists he has published a very readable book in which the principal interest is focused upon the social-medical

aspects of chronic illnesses in children. In the various chapters are discussed the mentally sick child, the mentally deficient child, children that are handicapped due to orthopedic, allergic, cardiac illnesses, to diabetes, epilepsy and tuberculosis. Special stress is laid upon mental care and physical treatment and rehabilitation. The book is full of valuable suggestions and it can be read with great profit by the clinician as well as by the general practitioner.

NEWS AND COMMENTS

Research Fellowships of the International Children's Centre

A number of fellowships for the academic year 1954—1955 will be available for research workers who may wish to work at the laboratories of the International Children's Centre, Paris.

At present the programme of research of the Centre is essentially connected with problems of anti-tuberculosis vaccination and anti-pertussis immunization.

The grants amount to 60,000 French francs per month.

Travelling expenses from their residence to Paris will have to be borne by the research fellows.

Research workers who wish to apply for a fellowship are requested to send their application together with their curriculum vitae, record of previous work and testimonials of their chiefs of service to Professor BUGNARD, International Children's Centre, Château de Longchamp, Paris 16 .

The Fourth Commonwealth Health and Tuberculosis Conference is scheduled to take place in London June 21—23, 1955.